VERIFICATION OF TRANSLATION

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1. That I am well acquainted with both the English and Japanese languages, and

2. That the attached document is a true and correct translation made by me to the best of my knowledge and belief of:

the specification of Japanese Patent Application numbered
Patent Application No. 2002-10413

Signature of translator

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[Article Name] Abstract 1

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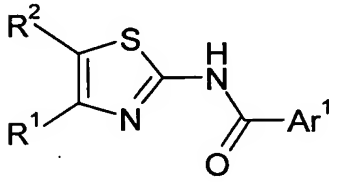
[Title of the invention] 2-ACYLAMINOTHIAZOLE DERIVATIVE AND SALT THEREOF

[Claims]

[Claim 1] A pharmaceutical composition for increasing platelets comprising a 2-acylaminothiazole derivative represented by the following general Formula (I) or a pharmaceutically acceptable salt thereof:

[Chemical Formula 1]



(I)

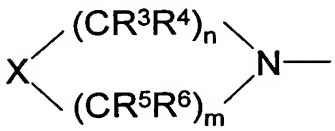
[wherein symbols have the following meanings.

Ar^1: optionally substituted aryl, monocyclic aromatic heterocycle, or bicyclic condensed heterocycle,

R^1: optionally substituted aromatic heterocycle, with the proviso that pyridyl is excluded,

R^2: a group represented by the following general Formula (II) or (III):

[Chemical Formula 2]



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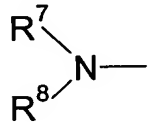


(III)

n: an integer of 1 to 3,

m: an integer of 1 to 2,

X: O, S, or a group represented by $N(R^9)$, or $C(R^{10})(R^{11})$,

R^3, R^4, R^5, R^6, R^9, R^{10} and R^{11}: which may be identical or different, -H; -OH; -O-lower alkyl; optionally substituted lower alkyl; optionally substituted cycloalkyl; optionally substituted aryl; optionally substituted aralkyl; optionally substituted aromatic heterocycle; optionally substituted heteroarylalkyl; optionally substituted nonaromatic heterocycle; lower alkenyl; lower alkylidene; -COOH; -COO-lower alkyl; -COO-lower alkenyl; -COO-lower alkylene-aryl; -COO-lower alkylene-aromatic heterocycle; carbamoyl or amino, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl which may be substituted with halogen, -OH, -O-lower alkyl or –O-aryl, and cycloalkyl; -NHCO-lower alkyl; or, oxo,

Wherein, in case n or m is an integer of 2 or more, CR^3R^4 and CR^5R^6 may be identical or different.

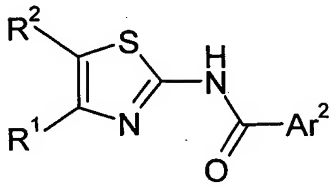
R^7 and R^8: which may be identical or different, -H, optionally substituted lower alkyl, optionally substituted cycloalkyl, or optionally substituted nonaromatic heterocycle.]

[Claim 2] The pharmaceutical composition according to Claim 1, wherein the pharmaceutical composition is used as a therapeutic agent for thrombocytopenia.

[Claim 3] The pharmaceutical composition according to Claim 1, wherein the pharmaceutical composition is a c-Mpl ligand.

[Claim 4] A 2-acylaminothiazole derivative represented by the following general Formula (IV) or a pharmaceutically acceptable salt thereof:

[Chemical Formula 3]



(I V)

[wherein symbols have the following meanings.

Ar^2: optionally substituted aryl or monocyclic aromatic heterocycle, optionally substituted bicyclic condensed heterocycle, with the proviso that indol is excluded,

R^1: optionally substituted aromatic heterocycle, with the proviso that pyridyl is excluded,

R^2: a group represented by the general Formula (II) or (III) in Claim 1.]

[Claim 5] The compound or pharmaceutically acceptable salt thereof according to Claim 4, wherein R^1 is optionally substituted thienyl, and R^2 is a group represented by the general Formula (II), (wherein n is 2, m is 2, and X is a group represented by $N(R^9)$, $C(R^{10})(R^{11})$).

[Claim 6] A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof according to Claim 4 or Claim 5 as an active ingredient.

[Detailed description of the invention]

[0001]

[Field of the invention]

The present invention relates to a novel 2-acylaminothiazole derivative or a salt thereof, which is useful as a medicament particularly in

the treatment of thrombocytopenia, and a medicament comprising the compound as an active ingredient.

[0002]

[Description of the Prior Art]

A platelet is anuclear blood cell playing an important role in physiological hemostasis and pathological thrombosis, and is continuously produced from megakaryocytes in a living body. The platelet is originated from pluripotent stem cells like other blood cells. Specifically, the pluripotent stem cell becomes megakaryocytic progenitor cell, from which megakaryoblasts, promegakaryocytes and megakaryocytes are formed. During the maturation of the megakaryocyte, premature megakaryocyte carries out only DNA synthesis without involving a cell division to become a polyploid. Thereafter, cytoplasm begins to mature to form a platelet separation membrane, and platelet is released by cytoplasm fragmentation.

In addition, since platelet decrease due to various hematopoietic dysfunctions in aplastic anemia, myelodysplastic syndrome, or chemotherapy or radiotherapy for malignant tumor and the like causes serious symptoms such as hemorrhage tendency, there have been many attempts for developing various technologies for increasing platelets for the purpose of treating them. At present, although a platelet transfusion is a powerful means for treating thrombocytepenia, sufficient amount of platelet cannot be provided, and it is difficult to sufficiently improve thrombocytepenia because of short life span of transfused platelet and the like. And, a platelet transfusion involves problems including viral infection, production of

alloantibodies, and Graft Versus Host Disease (GVHD) and the like. Thus, there is a demand for the development of a medicament for mitigating hematopoietic suppression caused by various conditions or therapies thereby promoting the recovery of platelet number.

[0003]

Meanwhile, it was reported that thrombopoietin (herein after referred to as 'TPO'), which is a c-Mpl ligand playing an important role in differentiation into megakaryocyte, was cloned, and that it stimulates differentiation and proliferation of megakaryocyte to promote production of platelet (Kaushansky K. et. al., Nature, 369, 568-571, 1994: Non Patent Document 1). Clinical tests on TPO as platelet increasing agent have already been carried out, and its availability and admissibility in human have been confirmed. However, because a neutralizing antibody was confirmed in a clinic test of PEG-rHuMGDF, a kind of TPO (163 N-terminal amino acids of native TPO modified with polyethyleneglycol) (Vadhan-Raj S, Semin Hematol., 37(suppl. 4), 28-34, 2000), there is a concern about immunogenicity of TPO. And, because TPO is a protein, it is decomposed in a digestive tract, and thus is not practical for an agent for oral administration. For the same reason, it is considered that low molecular peptide is also not practical for an agent for oral administration. Under these circumstances, the development of nonpeptide c-Mpl ligand, which has low immunogenicity and can be orally administrated, for the purpose of treatment of thrombocytepenia, is under progress.

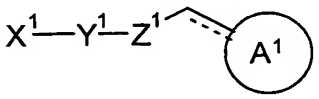
[0004]

As such compounds, benzazepine derivatives are disclosed in Japanese Laid-Open Patent Publication No. Hei 11-152276, acylhydrazone derivatives in WO 99/11262, diazonaphthalene derivatives in WO 00/35446, pyrrolocarbazole derivatives in WO 98/09967, pyrrolophenanthridine derivative in Japanese Laid-Open Patent Publication No. Hei 10-212289, and pyrrolophthalimide derivatives in Japanese Laid-Open Patent Publication No. Hei 2000-44562.

[0005]

And, it is described in WO 01/07423 that a compound represented by the following general Formula (VII) has an activity of increasing platelet:

[Chemical Formula 4]



(VI)

(wherein symbols are as defined in the above publication)

And, the above publication describes a compound wherein X^1 is optionally substituted thiazole, and Y^1 comprises –NHCO-. However, Ar^1 or Ar^2 of the compound of the present invention is not substituted with a substituent group having A^1 group such as thiazolyl group as in the above publication. And, the above publication does not mention in the Examples and the others a compound wherein 5 position of thiazole is directly substituted with a nitrogen atom.

[0006]

And, it is described in WO 01/53267 that a compound represented by the following general Formula (VIII) has an activity of increasing platelet:

[Chemical Formula 5]

$X^1—Y^1—Z^1—W^1$ (VII)

(wherein symbols are as defined in the publication)

The above publication describes a compound wherein X^1 is optionally substituted thiazole, and Y^1 comprises –NHCO-. However, Ar of the compound of the present invention is not substituted with a substituent group having W^1 group. And, the above publication does not mention in the Examples and the others a compound wherein 5 position of thiazole is directly substituted with a nitrogen atom.

[0007]

And, in addition to the WO01/07423 and WO01/53267, it is described in Japanese Patent Publication No. 3199451 that 2-acylaminothiazole compound has the effects of cholecystokinin and gastrin receptor agonist, and it is described in Chemical and Pharmaceutical Bulletin, 25, 9, 2292-2299, 1977 that 2-acylaminothiazole compound has anti-inflammatory effects. However, there is no description about platelet increasing activity.

[0008]

[Object of the invention]

Under these circumstances, there is a demand for the development of nonpeptide c-Mpl ligand that has low immunogenicity and can be orally administrated, for the purpose of treatment of thrombocytopenia.

[0009]

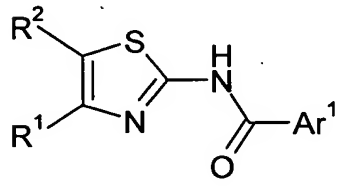
[Means to achieve the object]

The inventors, as results of assiduous studies on compounds having

activities of increasing platelets, discovered that novel 2-acylaminothiazole derivatives have excellent platelet increasing effects, and completed the present invention.

The present invention relates to a pharmaceutical composition for increasing platelets comprising a 2-acylaminothiazole derivative represented by the following general Formula (I) or a pharmaceutically acceptable salt thereof:

[Chemical Formula 6]



(I)

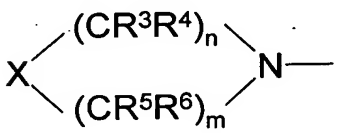
[wherein symbols have the following meanings.

Ar^1: optionally substituted aryl, monocyclic aromatic heterocycle, or bicyclic condensed heterocycle,

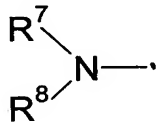
R^1: optionally substituted aromatic heterocycle, with the proviso that pyridyl is excluded,

R^2: a group represented by the following general Formula (II) or (III):

[Chemical Formula 7]



(II)



(III)

n: an integer of 1 to 3,

m: an integer of 1 to 2,

X: O, S, or a group represented by $N(R^9)$, or $C(R^{10})(R^{11})$,

R^3, R^4, R^5, R^6, R^9, R^{10} and R^{11}: which may be identical or different, -H; -OH; -O-lower alkyl; optionally substituted lower alkyl; optionally substituted cycloalkyl; optionally substituted aryl; optionally substituted aralkyl; optionally substituted aromatic heterocycle; optionally substituted heteroarylalkyl; optionally substituted nonaromatic heterocycle; lower alkenyl; lower alkylidene; -COOH; -COO-lower alkyl; -COO-lower alkenyl; -COO-lower alkylene-aryl; -COO-lower alkylene-aromatic heterocycle; carbamoyl or amino, each of which may be substituted with one or more groups selected from the group consisting of lower alkyl which may be substituted with halogen, -OH, -O-lower alkyl or –O-aryl, and cycloalkyl; -NHCO-lower alkyl; or, oxo,

wherein, in case n or m is an integer of 2 or more, CR^3R^4 and CR^5R^6 may be identical or different.

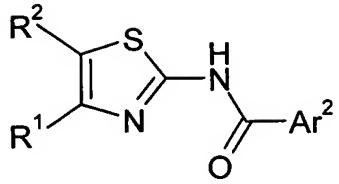
R^7 and R^8: which may be identical or different, -H, optionally substituted lower alkyl, optionally substituted cycloalkyl, or optionally substituted nonaromatic heterocycle.]

The present invention also relates to a platelet increasing agent represented by the general Formula (I) that is a therapeutic agent for thrombocytopenia, and a c-Mpl ligand.

[0010]

The present invention also relates to a 2-acylaminothiazole derivative represented by the general Formula (IV) or a pharmaceutically acceptable salt thereof.

[Chemical Formula 8]



(IV)

[wherein symbols have the following meanings.

Ar^2: optionally substituted aryl or monocyclic aromatic heterocycle, optionally substituted bicyclic condensed heterocycle, with the proviso that indol is excluded,

R^1: optionally substituted aromatic heterocycle, with the proviso that pyridyl is excluded,

R^2: a group represented by the general Formula (II) or (III) in Claim 1.]

Preferred is a 2-acylaminothiazole derivative represented by the general Formula (IV) or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted thienyl, and R^2 is a group represented by the general Formula (II), (wherein n is 2, m is 2, and X is a group represented by $N(R^9)$, $C(R^{10})(R^{11})$).

The present invention also relates to a pharmaceutical composition comprising the 2-acylaminothiazole derivative represented by the general Formula (IV) or a pharmaceutically acceptable salt thereof, or the 2-acylaminothiazole derivative represented by the general Formula (IV) or a pharmaceutically acceptable salt thereof wherein R^1 is optionally substituted thienyl, and R^2 is a group represented by the general Formula (II), (wherein n is 2, m is 2, and X is a group represented by $N(R^9)$, $C(R^{10})(R^{11})$), as an active ingredient.

[0011]

[Preferred embodiment of the invention]

The following describes the compound of the invention in detail.

In the definition of the general formula of the present invention, the term "lower" means a straight or branched carbon chain having 1 to 6 carbon atoms, unless otherwise indicated.

Thus, the "lower alkyl" means alkyl having 1to 6 carbon atoms, and its examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, hexyl, and the like, of which those having 1 to 3 carbon atoms such as methyl, ethyl, propyl, and isopropyl are preferred.

The 'lower alkenyl' means alkenyl having 2 to 6 carbon atoms, and its examples include ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like, of which those having 2 to 3 carbon atoms such as ethenyl, 1-propenyl, 2-propenyl and 3-propenyl are preferred.

The 'lower alkylidene' means alkylidene having 1 to 6 carbon atoms, and its examples include methylidene, ethylidene, propylidene, butylidene, pentylidene, hexylidene, and the like, of which those having 1 to 3 carbon atoms such as methylidene, ethylidene, 1-propylidene and 2-propylidene are preferred.

The 'lower alkylene' means a divalent group of alkyl having 1 to 6 carbon atoms, of which those having 1 to 4 carbon atoms such as methylene, ethylene, trimethylene, methylethylene, tetramethylene, dimethylmethylene and dimethylethylene are preferred.

[0012]

The 'cycloalkyl' means a carbon ring having 3 to 8 carbon atoms. Its examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, and the like.

The 'aryl' means a mono- to tri-cyclic aromatic ring having 6 to 14 carbon atoms, of which phenyl and naphthyl are preferred, and phenyl is more preferred.

The 'aralkyl' means the 'lower alkyl' substituted with the 'aryl', and its examples include benzyl, 1-phenethyl, 2-phenethyl, naphthylmethyl, 1-naphthylethyl, 2-naphthylethyl and the like.

[0013]

The 'monocyclic aromatic heterocycle' means a monovalent group of five- to six-membered aromatic heterocycle, which may comprise nitrogen, oxygen or sulfur atom, and its examples include thienyl, furyl, pyrrolyl, thiazolyl, oxazoylyl, imidazolyl, isothiazolyl, isoxazolyl, pyrazolyl, thiadiazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl and the like.

The 'aromatic heterocycle' means a monovalent group of aromatic heterocycle, a hetero ring which may have 1 to 4 hetero atoms, which may be identical or different, selected from the group consisting of nitrogen, oxygen and sulfur, and its examples include, in addition to the 'monocyclic aromatic heterocycle', indolyl, isoindolyl, indolizinyl, indazolyl, quinolyl, isoquinolyl, quinolidinyl, phthalazinyl, naphthylidinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzofuranyl, benzoxazolyl, 1,2-

benzoisoxazolyl, benzothienyl, benzothiazolyl, oxazolopyridyl, thiazolopyridyl and the like.

[0014]

The 'bicyclic condensed heterocycle' means a monovalent group of an aromatic heterocycle condensed with aryl or monocyclic aromatic heterocycle, or its partially hydrogenated ring, which may comprise nitrogen, oxygen or sulfur atom, and its example include indolyl, isoindolyl, indolizinyl, indazolyl, quinolyl, isoquinolyl, quinolidinyl, phthalazinyl, naphthylidinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzofuranyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothienyl, benzothiazolyl, oxazolopyridyl, thiazolopyridyl, indolinyl, isoindolinyl, 1,2-dihydroquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 3,4-dihydro-2H-1,4-benzoxazinyl, 1,4-dihydro-2H-3,1-benzoxazinyl, chromanyl, isochromanyl, benzoxolanyl, benzodioxolanyl, benzodioxanyl and the like.

[0015]

The 'heteroaryl alkyl' means the 'lower alkyl' substituted with the 'aromatic heterocycle', and its examples include thienylmethyl, furylmethyl, pyridylmethyl, thiazolylmethyl, oxazolylmethyl, imidazolylmethyl, thienylethyl, furylethyl, pyridylethyl and the like.

The 'non-aromatic heterocycle' means a monovalent group of nonaromatic heterocycle, which may have one or more hetero atoms, which are identical or different, selected from the group consisting of nitrogen, oxygen and sulfur, and its examples include azetidinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, azepinyl,

piperazinyl, homopiperazinyl, morpholinyl, thiomorpholinyl, and the like.

[0016]

The 'halogen' includes fluorine, chlorine, bromine, and iodine atoms.

The 'ligand' means a low molecular weight substance binding to an enzyme, receptor, protein, and the like, and includes agonist and antagonist, of which agonist is preferred.

[0017]

As substituent groups that can be used for the term "optionally substituted" or "which may be substituted", those commonly used as substituent groups for each group can be used, and each group may have one or more substituent groups.

[0018]

As the substituent groups that can be used for the "optionally substituted aryl, monocyclic aromatic heterocycle, or bicyclic condensed heterocycle" in the definition of Ar^1 and Ar^2, lower alkyl which may be substituted with one or more halogen atoms, halogen, oxo and a group represented by the general Formula (X) can be exemplified.

[Chemical Formula 9]

—B—C—A (X)

[wherein symbols have the following meanings.

-B-: -O-, -NH-, -N(R^{12})-, or a single bond

R^{12}: lower alkyl which may be substituted with one or more groups selected from the group consisting of halogen, -OH, -O-lower alkyl and cyano,

-C-: lower alkylene which may be substituted with one or more

groups selected from the group consisting of halogen, -OH, -O-lower alkyl and oxo, or a single bond,

-A: a group selected from the following (a) to (e)

(a) halogen, -OH, -O-lower alkyl, -OCO-lower alkyl, -COOH, -COO-lower alkyl, cyano, $-NHCONH_2$ or $-NHSO_2NH_2$.

(b) carbamoyl or amino, each of which may be substituted with one or two groups selected from the group consisting of lower alkyl and cycloalkyl.

(c) –NHCO-lower alkyl, -NHCOO-lower alkyl or $-NHSO_2$-lower alkyl, each of which may be substituted with –O-lower alkyl.

(d) –O-aryl which may be substituted with one or more groups selected from the group consisting of –OH, -O-lower alkyl and –O-lower alkylene-O-lower alkyl.

(e) aryl, aromatic heterocycle, nonaromatic heterocycle, -O-aralkyl, or –O-heteroarylalkyl, each of which may be substituted with one or more groups described in the following.

lower alkyl which may be substituted with one or more groups selected from the group consisting of halogen, -OH and –O-lower alkyl;

-OH; -O-lower alkyl; -O-lower alkylene-O-lower alkyl;

-COOH; -COO-lower alkyl; -CO-lower alkyl;

carbamoyl; N-(lower alkyl) or N,N-di(lower alkyl)carbamoyl; N-cycloalkyl or N,N-di(cycloalkyl)carbamoyl; N-(lower alkyl)-N-cycloalkylcarbamoyl; -CO-nonaromatic heterocycle; amino; N-(lower alkyl) or N,N-di(lower alkyl)amino; N-cycloalkyl or N,N-di(cycloalkyl)amino; N-(lower alkyl)-N-cycloalkylamino;

cyano; halogen; oxo,

with the proviso that when B is a single bond, A is –COOH, -COO-lower alkyl, optionally substituted carbamoyl, optionally substituted aryl, or optionally substituted aromatic heterocycle, C is methylene.

[0019]

As the substituent groups that can be used for 'optionally substituted aromatic heterocycle", "optionally substituted thienyl" in the definition of R^1, lower alkyl which may be substituted with one or more halogen atoms, -OH, -O-lower alkyl, -COOH, -COO-lower alkyl, carbamoyl or amino which may be substituted with 1 or 2 lower alkyl, cyano, nitro and halogen can be exemplified.

[0020]

As the substituent groups that can be used for 'optionally substituted lower alkyl' in the definitions of R^3, R^4, R^5, R^6, R^7,R^8, R^9, R^{10}, and R^{11}, -OH; -O-lower alkyl; -O-aryl; -COOH; -COO-lower alkyl; carbamoyl which may be substituted with 1 or 2 groups selected from the group consisting of lower alkyl and cycloalkyl; amino which may be substituted with 1 or 2 groups selected from the group consisting of lower alkyl and cycloalkyl; cyano; halogen; oxo; nonaromatic heterocycle which may be substituted with one or more groups selected from the group consisting of lower alkyl, -O-lower alkyl, -OH and halogen can be exemplified.

[0021]

As the substituent groups that can be used for 'optionally substituted cycloalkyl', 'optionally substituted aryl', 'optionally substituted aralkyl',

'optionally substituted aromatic heterocycle', 'optionally substituted heteroarylalkyl', 'optionally substituted nonaromatic heterocycle' in the definitions of R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11}, lower alkyl which may be substituted with one or more halogen atoms; -OH, ;-O-lower alkyl; -O-lower alkyl-O-lower alkyl; -COOH; -COO-lower alkyl; -CO-lower alkyl; carbamoyl which may be substituted with 1 or 2 groups selected from the group consisting of lower alkyl and cycloalkyl; amino which may be substituted with 1 or 2 groups selected from the group consisting of lower alkyl and cycloalkyl; cyano; halogen; oxo; nonaromatic heterocycle which may be substituted with one or more groups selected from the group consisting of lower alkyl, -O-lower alkyl, -OH and halogen, and the like can be exemplified.

[0022]

The compound of the present invention represented by the general Formula (I) or (IV) may comprise asymmetric carbon atoms depending on the kinds of substituent groups, and optical isomers based on the asymmetric carbon atom may exist. The compound of the present invention includes a mixture of these optical isomers or isolated one. And, tautomers may exist in the compound of the present invention, and the compound of the present invention includes these isomers as a mixture or an isolated one. As the tautomer, 2-hydroxypyridine and 2-pyridone can be exemplified.

[0023]

In addition, the compound of the present invention may form a salt, which is included in the present invention as long as pharmaceutically acceptable. Examples of the salt include addition salts with a mineral acid

such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethansulfonic acid, p-toluenesulfonic acid, aspartic acid, glutamic acid and the like; salts with an inorganic base such as sodium, potassium, magnesium, calcium and the like, or an organic base such as methylamine, ethylamine, ethanolamine, lysine, ornithine and the like; and ammonium salts, and the like. And, a hydrate and a solvate of the compound and its pharmaceutically acceptable salt of the present invention, and those having polymorphism are also included in the present invention. In addition, the compound of the present invention also includes a compound which is metabolized in a living body to be converted into the compound of the general Formula (I) or (IV) or its salt, so called prodrug. As groups forming the prodrug, those described in Prog. Med., 5; 2157-2161, 1985. and Kwangchun, 1990, "Development of medicine" Vol. 7, Molecular Design, pp 163-198 can be exemplified.

[0024]

(Production Method)

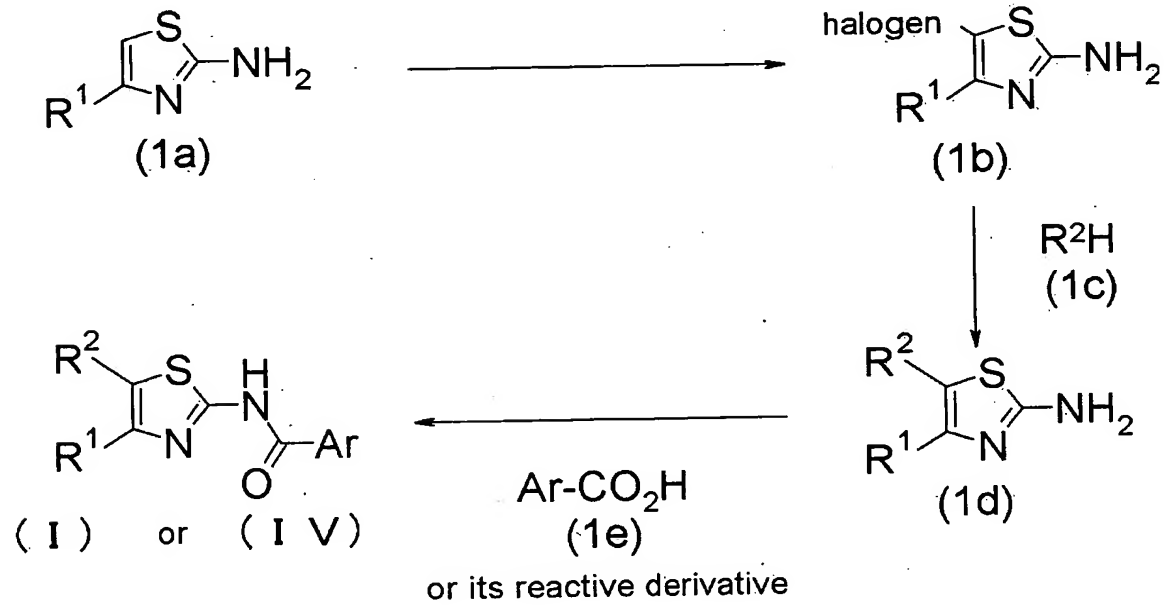
The compound and its pharmaceutically acceptable salt of the present invention can be prepared by various known synthesis methods, using characteristics based on its basic backbone or the kinds of substituent groups. The following describes representative preparation methods. And, according to the kinds of functional groups, it is advantageous in some cases

in terms of preparation technique to substitute a functional group with a suitable protection group, i.e., a group that can be easily converted into the functional group, in the step of raw material or intermediate. Then, if necessary, the protection group is removed to obtain a desired compound. Examples of the functional group include hydroxyl, carboxyl and amino group, and examples of the protection group include those described in "Protective Groups in Organic Synthesis ", third edition, edited by Greene and Wuts. It is preferable to suitably use them depending on reaction conditions.

[0025]

(First production method)

[Chemical Formula 10]



(wherein R^1, R^2, Ar are as defined in the foregoing)

In this method, a compound of the general Formula (I) or (IV) is

prepared by the amidation of a compound (1d) or its salt with a compound (1e) or its reactive derivative by a general method, and then, if necessary, removing a protection group.

As the reactive derivatives of the compound (1e), common ester such as methylester, ethylester, tert-butyl ester and the like; acid halide such as acid chloride, acid bromide, and the like; acid azide; active ester with N-hydroxybenzotriazole, p-nitrophenol or N-hydroxysuccinimide or the like; symmetrical acid anhydride; acid anhydride mixture with alkyl carbonate, p-toluenesulfonic acid or the like can be exemplified.

[0026]

In case the compound (1e) is reacted as a free acid, or the active ester or acid halide is reacted without isolated, and the like, it is suitable to carry out the reaction using a condensing agent such as dicylcohexylcarbodiimide, carbonyldiimidazole, diphenylphosphorylazide, diethylphosphorylcyanide, or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl), and phosphorous oxychloride in pyridine solvent.

[0027]

The reaction is, although varies depending on the reactive derivatives or condensing agent, carried out in an inert organic solvent such as halogenated hydrocarbon including dichloromethane, dichloroethane, chloroform and the like; aromatic hydrocarbon including benzene, toluene, xylene and the like; ether including ether, tetrahydrofuran (THF) and the like; ester including ethyl acetate; N,N-dimethylformamide (DMF) or dimethylsulfoxide (DMSO), and the like, under cooling, cooling to room

temperature, or room temperature to heating.

[0028]

In order to progress the reaction smoothly, it is advantageous in some cases to employ an excess amount of the compound (1e) or carry out the reaction in the presence of a base such as N-methylmorpholine, trimethylamine, triethylamine, N,N-dimethylaniline, pyridine, 4-(N,N-dimethylamino)pyridine, picoline, lutidine, and the like. And, a salt consisting of strong acid and weak base such as pyridine hydrochloride, pyridine p-toluenesulfonate, N,N-dimethylaniline hydrochloride and the like can be used. Pyridine can also be used as a solvent.

Particularly, it is advantageous to carry out the reaction in a solvent such as acetonitrile or DMF using a base such as pyridine or N,N-dimethylaniline, or using pyridine as a solvent.

[0029]

The starting material (1d) used in the reaction can be prepared by synthesizing a compound (1b) by halogenation of 5 position of a compound (1a) and then reacting the compound (1b) with a compound (1c). The compound (1b) can also be used in subsequent reaction without isolated.

[0030]

As a halogenation agent, those commonly used for halogen substitution reaction of hydrogen on aromatic ring can be used. Halogen atom such as chlorine, bromine and the like, dioxanedibromide, phenyltrimethylammonium tribromide, pyridine such as pyridinium hydrobromide perbromide, pyrrolidonehydrotribromide and the like,

perbromide such as α-pyrrolidone, quaternary ammonium, dioxane and the like are appropriate. Imide type halogenation agent such as N-bromosuccinimide, N-chlorosuccinimide and the like, hydrogen halide such as hydrochloric acid, hydrobromic acid and the like, a metal agent such as copper (II) halide including copper bromide (II), copper chloride (II) and the like can also be used.

[0031]

In case a halogen or perbromide is used, the compound (1a) can be reacted in an inert organic solvent such as halogenated hydrocarbon; ether; alcohol including methanol (MeOH), ethanol (EtOH), 2-propanol, ethyleneglycol and the like; aromatic hydrocarbon; acetic acid; ester including ethyl acetate (EtOAc) and the like. If necessary, the reaction may be carried out in the presence of a small amount of a catalyst such as hydrogen halide. It is preferable to carry out the reaction at -30 ℃ to reflux temperature of the used solvent.

In case hydrogen halide is used as a halogenation agent, the compound (1a) can be reacted therewith in an acid solution or a base solution such as sodium hydroxide aqueous solution, and the reaction is preferably carried out at -30 ℃ to reflux temperature of the used solvent. And, in case a metal agent is used as a halogenation agent, the compound (1a) is generally dissolved in an inert organic solvent such as halogenated hydrocarbon, ether, alcohol, aromatic hydrocarbon, acetic acid, ester, and the like, or water, or a mixture thereof to react with the agent, and if necessary, it is advantageous to carry out the reaction in the presence of a small

amount of a catalyst such as hydrogen halide, under room temperature to heating.

[0032]

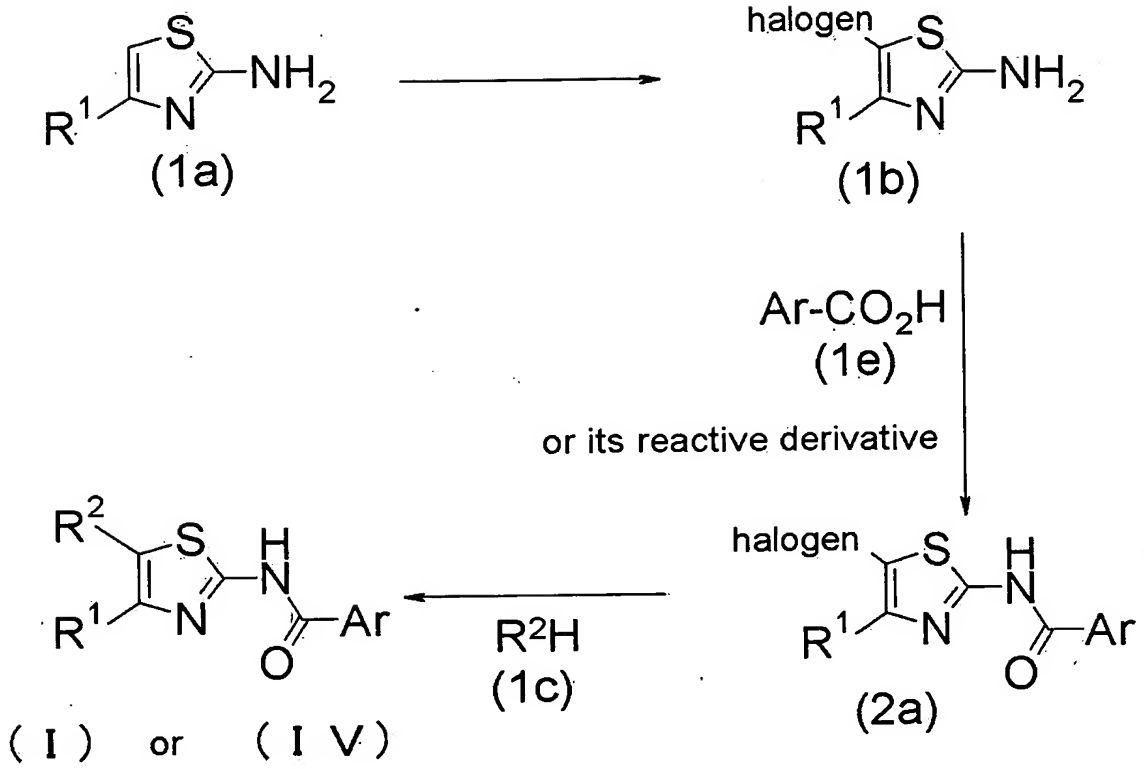
The thus obtained compound (1b) is reacted with the compound (1c) in a non-protonic polar solvent such as DMF, N-methyl-2-pyrrolidone, DMSO and the like, an inert organic solvent such as halogenated hydrocarbon, ether, aromatic hydrocarbon, or water, or a mixture thereof to prepare a compound (1d). The reaction is preferably carried out at room temperature to reflux temperature of the used solvent.

In order progress the reaction smoothly, it is advantageous in some cases to employ an excess amount of the compound (1e) or carry out the reaction in the presence of a base such as N-methylmorpholine, triethylamine, diethylisopropylamine, N,N-dimethylaniline, pyridine, 4-(N,N-dimethylamino)pyridine, picoline, lutidine and the like.

[0033]

(Second production method)

[Chemical Formula 11]



In this method, a compound (2a) is synthesized by the amidation of the compound (1b) synthesized by the first production method with a compound (1e) or its reactive derivative, and then reacted with a compound (1c), and if necessary a protection group is removed to prepare the compound (I) or (IV) of the present invention.

Any step can be carried out in accordance with the processes of the first production method.

[0034]

The thus produced compound of the present invention is isolated and purified as its free form or as a salt thereof. A salt of the compound (I) can be produced by subjecting it to a usual salt formation reaction. The

isolation and purification are carried out by usual chemical operations such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, various types of chromatography and the like.

Various types of isomers can be separated by usual method using the difference in physicochemical properties among isomers. For example, racemic mixture can be separated by a general racemic mixture resolution method, e.g., a method in which it is converted into diastereomer salts with an optically active acid such as tartaric acid and the like and then subjected to optical resolution. And, diastereomers can be separated by fraction crystallization or various types of chromatography or the like. And, optically active compounds can be prepared using appropriate optically active starting materials.

[0035]

[Effect of the invention]

The compound and its salt of the present invention have excellent effects of increasing platelets. Thus, the compound of the present invention is useful in the treatment and/or prevention of thrombocytopenia due to aplastic anemia, myelodysplastic syndrome, chemotherapy or radiotherapy for malignant tumor, idopathic thrombocytopenic purpura, liver disease, HIV, and the like. In case thrombocytopenia is likely to be caused by chemotherapy or radiotherapy, it is possible to administrate the compound of the present invention prior to carrying out the therapy.

[0036]

Pharmaceutical efficacy of the compound of the present invention was

confirmed by the following tests.

Effects of promoting the formation of megakaryocytic colonies

Human $CD34^+$ cells were cultured at 37 ℃ for 10-14 days, in the presence of tested materials, in a 2 well chamber slide, using MegaCult™-C (Stem Cell Technologies). In accordance with the attached instructions, dehydration, fixing, and staining with anti-human glycoprotein IIb/IIIa antibody were carried out. A group of 3 or more of stained megakaryocytes was regarded as 1 colony, and the number of colonies per 1 well was measured by a microscope.

From these results, it has been confirmed that the compound of the present invention has excellent effects of promoting the formation of megakaryocytic colonies.

[0037]

A pharmaceutical composition of the present invention can be prepared by generally used methods using one or more kinds of the compound of the present invention of the general Formula (I) or (V) and pharmaceutical carriers, fillers and other additives generally used in the preparation of medicaments. It may be administrated either by oral administration through tablets, pills, capsules, granules, powders, solutions and the like, or by parenteral administration through injections such as intravenous injection, intramuscular injection and the like, or through suppositories, or pernasal, permucosal or percutaneous preparations and the like.

[0038]

The solid composition for use in the oral administration according to

the present invention is used in the forms of tablets, powders, granules and the like. In such a solid composition, one or more active substances are mixed with at least one kind of inert diluent such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, metasilicate or magnesium aluminate. In the usual way, the composition may contain additives other than the inert diluent, which include a lubricant such as magnesium stearate, a disintegrating agent such as calcium cellulose glycolate, a stabilizing agent such as lactose and a solubilization assisting agent such as glutamic acid or aspartic acid. As occasion demands, tablets or pills may be coated with a sugar coat or a film of gastrosoluble or enterosoluble substance such as sucrose, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, or the like.

[0039]

The liquid composition for oral administration includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like and contains a generally used inert diluent such as purified water or ethanol. In addition to the inert diluent, this composition may also contain auxiliary agents such as a moistening agent and a suspending agent, as well as a sweetener, a flavor, and aromatic and an antiseptic.

[0040]

The injections for parenteral administration include aseptic aqueous or non-aqueous solutions, suspensions and emulsions. Examples of the aqueous solutions and suspensions include distilled water for injection use

and physiological saline. Examples of the non-aqueous solutions and suspensions include plant oil such as propylene glycol, polyethylene glycol, olive oil or the like, alcohol such as ethanol, polysorbate 80 (trade name) and the like. Such a composition may further contain auxiliary agents such as an antiseptic, a moistening agent, an emulsifying agent, a dispersing agent, a stabilizing agent (e.g., lactose) and a solubilization assisting agent (e.g., glutamic acid or aspartic acid. These compositions are sterilized for example by filtration through a bacteria retaining filter, blending of a germicide or irradiation. Alternatively, they may be used by firstly making into sterile solid compositions and dissolving them in sterile water or a sterile solvent for injection use prior to their use.

[0041]

In the case of oral administration, a daily dose is approximately 0.0001~50 mg/kg per body weight, preferably approximately 0.001~10 mg/kg, and more preferably approximately 0.01~1 mg/kg, and the daily dose is administered once a day or by dividing it into 2 to 4 doses per day. In the case of intravenous administration, a daily dose is approximately 0.0001~1 mg/kg per body weight, preferably approximately 0.0001~0.1 mg/kg, and the daily dose is administered once a day or by dividing it into plural doses per day. The dose is appropriately decided by taking symptoms, age and sex of the patient to be treated and the like into consideration.

[0042]

[Example]

The following describes the invention more illustratively with

reference to examples, but the present invention is not limited to these examples. In this connection, novel materials are included in the starting materials to be used in the examples, and production methods of the starting materials from known materials are described as reference examples.

[0043]

Reference Example R1

To a solution of 4.18 g of 4-chloro-2-acetylthiophene in 30 ml of diethylether, 1.5 ml of bromine was added under ice cooling, and the mixture was stirred at room temperature for 2 hours. Water was added to the reaction solution to separate liquid, and the obtained organic layer was washed with saturated brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain brominated compound. To a solution of the brominated compound in 30 ml of EtOH, 2.1 g of thiourea was added at room temperature, and the mixture was stirred at 80 ℃ overnight. The thus precipitated solid was filtered to obtain a solution, which was evaporated under reduced pressure, and chloroform was added, and then an organic layer was washed with aqueous potassium carbonate and brine, and dried over sodium sulfate. The residue obtained by the evaporation of the solvent under reduced pressure was washed with hexane:EtOAc = 1:1 to obtain 2.57 g of 2-amino-4-(4-chlorothiophen-2-yl)thiazole.

[0044]

Compound of Reference Examples R2~R8 as shown in Table 1 were synthesized in the same manner as described in Reference Example R1,

employing each corresponding starting material.

[0045]

Symbols in the Table have the following meanings.

Rf: Reference Example number, Ex: Example number

Salt: salt (HCl: hydrochloride, AcOH: acetate, TFA: trifluoroacetate, no description: free form)

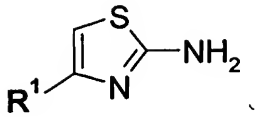
Data: physical data (MS: FAB-MS(M+H)+; MN:FAB-MS(M-H)-; NMR: peaks δ (ppm) in ^{1}H-NMR using $(CH_3)_4Si$ as an internal standard, and DMSO-d_6 as measuring solvent unless otherwise indicated)

Syn: production method (The number indicates Reference Example or Example number used for synthesis)

R^1, R^2, Ar: substituent groups in the general Formula (Me: methyl, Et: ethyl, nPr: normal propyl, iPr: isopropyl, nBu: normal butyl, tBu: tertiary butyl, cBu: cyclobutyl, cPen : cyclopentyl, nHex: normal Hexyl, cHex: cyclohexyl, cHep: cycloheptyl, Ph: phenyl, Bn: benzyl, The: thienyl, Fur: furanyl, Py: pyridyl, Mor: morpholin-4-yl, Ac: acetyl, Ms: methanesufonyl, Imd: imidazol-1-yl, pipe: piperidinyl, pipa: piperazinyl, TBS: tertiary butyl dimethylsilyl, di: di (2 of the corresponding substituent groups substitute), The number before the substituent group indicates substitution position. Thus, for example, 5-Cl-3-The indicates 5-chlorothiophen-3-yl, 4-cHex-1-pipa 4-cyclohexylpiperazin-1-yl)

[0046]

[Table 1]



Rf	Syn	R^1	Data
R1	R1	4-Cl-2-The	MS;217.
R2	R1	5-Cl-3-The	MS;217.
R3	R1	5-F-2-The	MS;201.
R4	R1	3-F-2-The	MS;201.
R5	R1	5-Me-2-The	MS;197.
R6	R1	4-Me-2-The	MS;197.
R7	R1	4-F-5-Cl-2-The	MS;235.
R8	R1	4-F-2-The	MS;201.

[0047]

Reference Example R9

To a solution of 0.5g of the compound of Reference Example R1 in 5 ml of DMF, 0.45 g of N-bromosuccinimide was added under ice cooling, and the mixture was stirred at the same temperature for 50 minutes. To the reaction mixture, 0.6 g of cyclohexylpiperazine and 0.6 ml of triethylamine were sequentially added, and the mixture was stirred at 70 ℃ for 3 days. The solvent was evaporated under reduced pressure, chloroform was added to the residue, and then the organic layer was washed with aqueous potassium carbonate and brine, and dried over sodium sulfate. The residue obtained by the evaporation of the solvent under reduced pressure was purified by a silica gel column chromatography (elute: hexane-EtOAc = 1:1) to obtain 300 mg of 2-amino-4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)thiazole.

[0048]

Reference Example R10

To a solution of 1.50 g of 2-amino-4-(5-chlorothiophen-2-yl) in 30 ml of THF, 0.36 ml of bromine was added dropwise, and the mixture was stirred

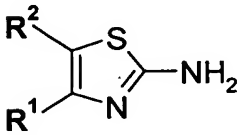
at room temperature for 3 hours. After the solvent was evaporated, 20 ml of DMF, 1.68 g of 4-propylidenepiperidine hydrochloride and 4.82 ml of triethylamine were added thereto, and the mixture was stirred at 75 ℃ for 3 days. The solvent was evaporated under reduced pressure, EtOAc was added to the residue, and then the organic layer was washed with saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. After the evaporation of the solvent, the obtained residue was purified by silica gel column chromatography (elute: hexane-EtOAc = 5:1-4:1) to obtain 1.23 g of 2-amino-4-(5-chlorothiophen-2-yl)-5-(4-propylidenepiperidin-1-yl)thiazole.

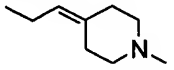
[0049]

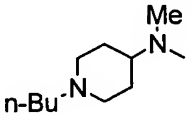
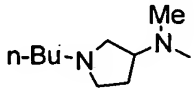
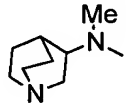
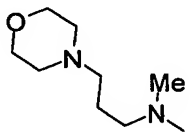
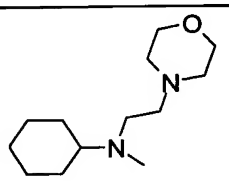
Compounds of Reference Examples R11-R34 as shown in Table 2 were synthesized in the same manner as described in Reference Example R9 or R10, employing each corresponding starting material.

[0050]

[Table 2]



Rf	Syn	R^1	R^2	Data
R9	R9	4-Cl-2-The	4-cHex-1-pipa	MS;383.
R10	R10	5-Cl-2-The		FAB-MS(M)$^+$;339.
R11	R10	5-Me-2-Fur	4-cHex-1-pipa	MS;347.
R12	R10	3-Cl-2-The	4-cHex-1-pipa	MS;383.
R13	R10	5-Cl-3-The	4-cHex-1-pipa	MS;383.
R14	R10	5-Cl-2-The	4-cHex-1-pipa	MS;383.
R15	R10	5-Br-2-The	4-cHex-1-pipa	MS;427,429.
R16	R9	5-F-2-The	4-cHex-1-pipa	MS;367.
R17	R9	4-Br-2-The	4-cHex-1-pipa	MS;427,429.

R18	R10	5-Me-2-The	4-cHex-1-pipa	MS;363.
R19	R9	4-Me-2-The	4-cHex-1-pipa	MS;363.
R20	R10	3-F-2-The	4-cHex-1-pipa	MS;367.
R21	R10	5-Cl-2-The	4-nPr-1-pipe	MS;342.
R22	R9	4-Cl-2-The	4-nPr-1-pipe	MS;342.
R23	R9	4-Cl-2-The		MS;385.
R24	R9	4-Cl-2-The	4-(allylO_2C)-1-pipa	MS;385.
R25	R9	4-Cl-2-The	3-(4-nPr-1-pipe)- azetidin-1-yl	MS;397.
R26	R9	4-Cl-2-The	4-Mor-1-pipe	MS;385.
R27	R9	4-Cl-2-The		MS;371.
R28	R9	4-Cl-2-The		MS;355.
R29	R9	4-F-5-Cl-2-The	4-cHex-1-pipa	MS;401.
R30	R9	4-Cl-2-The	4-nPr-1-pipa	MS;343.
R31	R9	4-Cl-2-The	Mor	MS;302.
R32	R9	4-F-2-The	4-cHex-1-pipa	MS;367.
R33	R9	4-Cl-2-The		MS;373.
R34	R9	4-Cl-2-The		MS;427.

[0051]

Reference Example R35

To a solution of 2.50 g of 3-chloro-4-hydroxybenzoic acid methyl ester in 25 ml of DMF, 2.78 g of potassium carbonate and 4.31 ml of 2-(tert-butyldimethylsilyloxy)ethylbromide were added, and the mixture was stirred at 50 ℃ for 15 hours. The solvent was evaporated, EtOAc was added to the residue, and the organic layer was washed with water and brine and

dried over sodium sulfate. After the evaporation of the solvent, the obtained residue was purified by silica gel column chromatography (eluent: hexane-EtOAc = 10:1~5:1) to obtain 4.88 g of 4-[2-(tert-butyldimethylsilyloxy)ethoxy]-3-chlorobenzoic acid methyl ester.

[0052]

Reference Example R36

To a solution of 1.5 g of 3-chloro-4-hydroxybenzoic acid methyl ester in 20 ml of THF, 1.8 ml of 1-tert-butoxy-2-propanol, 3.16 g of triphenylphosphine and 1.9 ml of diethylazodicarboxylate were added, and the mixture was stirred at room temperature for 1 hour. After the evaporation of the solvent under reduced pressure, the obtained residue was purified by silica gel column chromatography (eluent: hexane-EtOAc = 100:1~5:1) to obtain 2.3 g of 4-(1-tert-butoxy-2-propoxy)-3-chlorobenzoic acid methyl ester.

[0053]

Reference Example R37

4.0 g of 6-quinolinecarboxylic acid was suspended in 30 ml of MeOH, 2.0 ml of conc. sulfate was added under ice cooling, and the mixture was stirred at 70 ℃ for 22 hours. The reaction solution was concentrated under reduced pressure, and the residue was mixed with water and neutralized with potassium carbonate. The thus precipitated solid was filtered and dried to obtain 4.28 g of 6-quinolinecarboxylic acid methyl ester. 0.5 g of the obtained ester body was dissolved in 5 ml of formamide, 0.15 ml of conc. sulfate, 0.05 g of ferrous sulfate hepta-hydrate, and 0.4 ml of 31%

hydrogen peroxide were sequentially added thereto, and the mixture was stirred at 80 ℃ for 50 minutes. The reaction solution was mixed with water and alkalinized with potassium carbonate. 10% MeOH-chloroform was added, and insoluble matter was filtered using celite. The obtained filtrate was separated, the obtained organic layer was dried over anhydrous sodium sulfate and concentrated, and the obtained residue was washed with EtOH to obtain 0.15 g of 6-methoxycarbonyl-2-quinolinecarboxamide.

[0054]

Reference Example R38

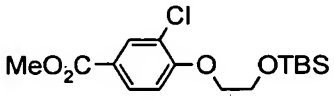
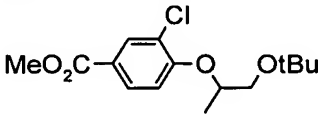
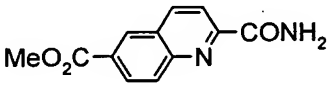
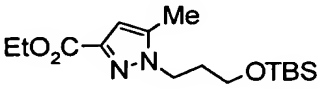
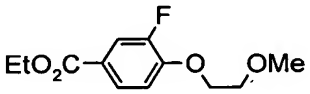
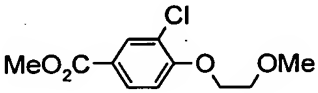
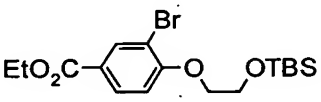
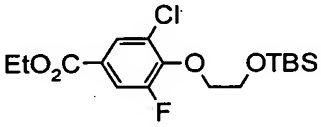
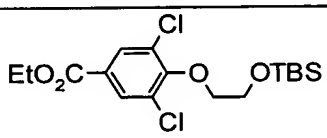
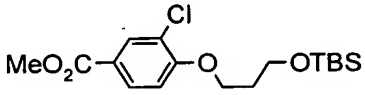
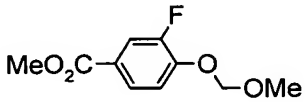
To a solution of 1.96 g of 5-methylpyrazole-3-carboxylic acid ethyl ester in 40 ml of DMF, 2.64 g of potassium carbonate and 3.53 ml of 3-(tert-butyldimethylsilyloxy)propylbromide were added, and the mixture was stirred at 50 ℃ for 18 hours. The solvent was evaporated, EtOAc was added to the residue, and the organic layer was washed with water and brine and dried over sodium sulfate. After the evaporation of the solvent, the obtained residue was purified by silica gel column chromatography (eluent: hexane-EtOAc = 15:1~5:1) to obtain 1.39 g of 1-[3-(tert-butyldimethylsilyloxy)propoxy]-5-methylpyrazole-3-carboxylic acid ethyl ester.

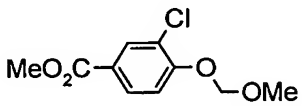
[0055]

Compounds of Reference Examples R39-R46 as shown in Table 3 were synthesized in the same manner as described in Reference Example R35, employing each corresponding starting material.

[0056]

[Table 3]

Rf	Syn	structure	Data
R35	R35		MS;345.
R36	R36		MS;301.
R37	R37		MS;231.
R38	R38		MS;327.
R39	R35		MS;243.
R40	R35		MS;245.
R41	R35		MS;403,405.
R42	R35		NMR($CDCl_3$);0.05-0.13(6H,m),0.82-0.93(9H,m),1.40(3H,t,J=7.1Hz),3.97(2H,t,J=5.1Hz),4.28-4.34(2H,m),4.37(2H,q,J=7.1Hz),7.68(1H,dd,J=2.0,11.6Hz),7.87(1H,t,J=2.0Hz)
R43	R35		MS;393.
R44	R35		MS;359.
R45	R35		GC-MS$(M)^+$;214.

R46	R35		MS;231.

[0057]

Reference Example R47

To a solution of 2.16 g of the compound of Reference Example R35 in MeOH 20ml-THF 15 ml, 7.5 ml of 1M NaOH aq was added, and the mixture was stirred at room temperature for 3 days. The solvent was evaporated, and the residue was acidified with 5% potassium hydrogensulfate aq. and extracted with chloroform-2-propanol (3:1). The organic layer was washed with brine, and dried over sodium sulfate, and then the solvent was evaporated to obtain 1.17 g of 4-[2-(tert-butyldimethylsilyloxy)ethoxy]-3-chlorobenzoic acid.

[0058]

Reference Example R48

To 1.56 g of 3,4,5-trifluorobenzoylchloride, 6.32 ml of 2-methoyethanol and 6.53 g of cesium carbonate were added, and the mixture was stirred at 100 ℃ for 20 hours. The reaction solution was mixed with 50 ml of THF and filtered, and the filtrate was evaporated to obtain 4.36 g of colorless solid. The solid was dissolved in 15 ml of THF, 3.16 ml of 2-methoxyethanol and 1.35 g of potassium tert-butoxide were added thereto, and the mixture was stirred at room temperature for 4 days. The reaction solution was mixed with 5% potassium hydrogensulfate aq. and extracted with EtOAc, and then, the organic layer was washed with brine and dried over sodium sulfate. The solvent was evaporated to obtain 1.76 g of 3,5-difluoro-4-(2-

methoxyethoxy)benzoate.

[0059]

Reference Example R49

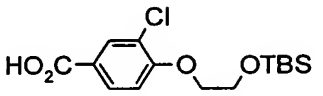
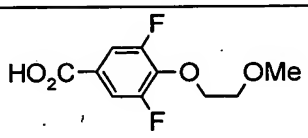
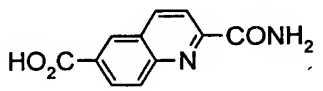
0.3 g of the compound of Reference Example R37 was dissolved in 10 ml of a mixed solvent of THF-MeOH (1:1), and 1.5 ml of 1M NaOH aq. was added at room temperature, and the mixture was stirred at the same temperature for 3 days. The reaction solution was concentrated under reduced pressure, mixed with water and neutralized with 1.5 ml of 1M HCl aq. The thus obtained solid was filtered and dried to obtain 0.29 g of 2-carbamoylquinoline-6-carboxylic acid.

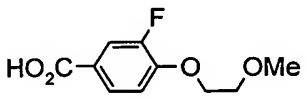
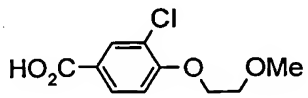
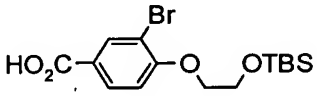
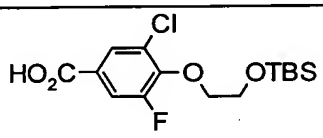
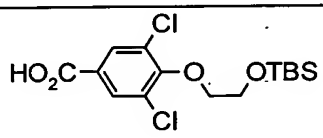
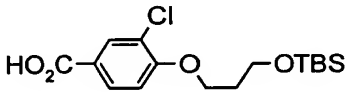
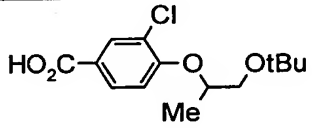
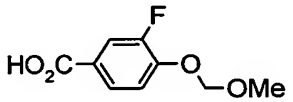
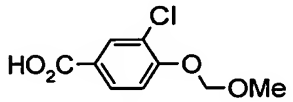
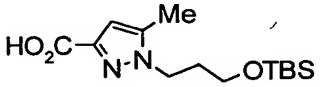
[0060]

Compounds of Reference Examples R50-R59 as shown in Table 4 were synthesized in the same manner as described in Reference Example R47, employing each corresponding starting material.

[0061]

[Table 4]

Rf	Syn	structure	Data
R47	R47		MN;329.
R48	R48		MN;231.
R49	R49		MN;215.

R50	R47		MN;213.
R51	R47		MN;229.
R52	R47		MN;373,375.
R53	R47		NMR($CDCl_3$);0.05-0.15(6H,m),0.85-0.92(9H,m),3.97(2H,t,J=5.2Hz),4.32-4.37(2H,m),7.73(1H,dd,J=2.0,11.2Hz),7.93(1H,t,J=2.0Hz).
R54	R47		MN;363.
R55	R47		MN;343.
R56	R47		MS;287.
R57	R47		MN;199.
R58	R47		MS;217.
R59	R47		MN;297.

[0062]

Example 1

To a solution of 500 mg of the compound of Reference Example R14 in 10 ml of DMF, 300 mg of 2-methoxyisonicotinic acid, 376 mg of WSC·HCl,

and 265 mg of HOBt were added, and the mixture was stirred at room temperature for 4 days. The solvent was evaporated, and the residue was mixed with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, and dried over sodium sulfate. After the evaporation of the solvent, the residue was purified by a silica gel column chromatography (hexane-EtOAc = 8:1~2:1) and dissolved in 10 ml of EtOAc, 0.46 ml of 0.4M HCl-EtOAc solution was added thereto, and the mixture was stirred for a while, and then the produced precipitate was collected by filtration to obtain 72 mg of N-[4-(5-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)thiazol-2-yl]-2-methoxyisonicotinamide hydrochloride.

[0063]

Example 2

To a solution of 342 mg of the compound of Reference Example R21 in 10 ml of DMF, 306 mg of 2-methoxyisoncotinic acid, 383mg of WSC·HCl, 270 mg of 1-hydroxybenzotriazole and 244mg of 4-(dimethylamino)pyridine were added, and the mixture was stirred at 50 ℃ for 3 days. The solvent was evaporated, and the residue was mixed with EtOAc and washed with saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. After evaporation of the solvent, the obtained residue was purified by silica gel column chromatography (hexane-EtOAc = 8:1), and dissolved in 30 ml of EtOAc, 4.1 ml of 0.1 M hydrochloride-EtOAc were added thereto, and the mixture was stirred, and then the produced precipitate was collected by filtration to obtain 120 mg of N-[4-(5-chlorothiopheny-2-yl)-5-(4-propylpiperidin-1-yl)thiazol-2-yl]-2-methoxyisonicotinamide hydrochloride.

[0064]

Example 3

To a solution of 383 mg of the compound of Reference Example R9 in 10 ml of pyridine, 397 mg of the compound of Reference Example R47 were added, 0.10 ml of phosphorous oxychloride were added at -25 ℃, the temperature was elevated to room temperature, and the mixture was stirred for 12 hours. The solvent was evaporated, the residue was mixed with water and potassium carbonate, and extracted with chloroform, and the organic layer was washed with brine, and dried over sodium sulfate. The solvent was evaporated, and the obtained residue was purified by silica gel column chromatography (hexane-EtOAc = 10:1~3:1) to obtain 187 mg of 4-[2-(tert-butyldimethylsilyloxy)ethoxy]-3-chloro-N-[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)thiazol-2-yl]benzamide.

[0065]

Example 4

To a solution of 100 mg of the compound of Example 65 in 5 ml of EtOH, 0.2 ml of 4M HCl-EtOAc solution was added, and the mixture was stirred for 27 hours. To the reaction solution, chloroform was added, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over sodium sulfate. After the evaporation of the solvent, the obtained residue was purified by a silica gel column chromatography (chloroform-MeOH = 100:1~5:1) and dissolved in 15 ml of MeOH, 10 ml of 4M HCl-EtOAc solution was added thereto, and the mixture was stirred for a while. Then, the solvent was evaporated under reduced pressure, and the residue was washed

with diethylether to obtain 28 mg of 5-chloro-N-[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)thiazol-2-yl]-6-hydroxynicotinamide hydrochloride.

[0066]

Example 5

To 183 mg of the compound of Example 67, 5 ml of trifluoroacetic acid was added, and the mixture was stirred for 40 hours. Then, the solvent was evaporated under reduced pressure, and the obtained residue was purified by a silica gel column chromatography (chloroform-MeOH=100:1~20:1) to obtain 50 mg of 3-chloro-N-[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)thiazol-2-yl]-4-(1-hydroxy-2-propoxy)benzamide trifluoroacetate.

[0067]

Example 6

0.34 g of the compound of Example 52 was suspended in 5 ml of MeOH, 1 ml of conc. HCl was added thereto under ice cooling, and the mixture was stirred at 50 ℃ overnight. To the reaction solution, 0.5 ml of conc. HCl was added again, and the mixture was stirred at 50 ℃ for 5 hours and 60 ℃ overnight. The reaction solution was cooled to a room temperature, and the thus precipitated solid was filtered and dried to obtain 0.33 g of N-[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)thiazol-2-yl]-3-fluoro-4-hydroxybenzamide hydrochloride.

[0068]

Example 7

187 mg of the compound of Example 3 was dissolved in 10 ml of MeOH, 3.5 ml of conc. HCl was added, and the mixture was stirred for 18 hours. Then, the thus produced precipitate was filtered and washed with diethylether to obtain 90 mg of 3-chloro-N-[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)thiazol-2-yl]-4-(2-hydroxyethoxy)benzamide hydrochloride.

[0069]

Example 8

To a solution of 5.23 g of the compound of Example 27 in 100 ml of THF, 17.0 g of tributyltin hydride was added at 0 ℃, and the mixture was cooled to -78 ℃. And, 670 mg of tetrakis(triphenylphosphine)palladium was added thereto, the temperature was slowly elevated to room temperature, and the mixture was stirred for 1.5 hours. The reaction solution was mixed with 1.6 ml of acetic acid and stirred at room temperature for 15 minutes. Then, the solvent was evaporated under reduced pressure, hexane was added to the obtained residue, and the thus formed precipitate was collected by filtration and dried under reduced pressure to obtain 4.30 g of N-[4-(4-chlorothiophen-2-yl)-5-(piperazin-1-yl)thiazol-2-yl]-2-methoxyisonicotinamide acetate.

[0070]

Example 9

0.15 g of the compound of Example 19 was dissolved in 5.0 ml of THF, total 1.3 ml of butyl lithium (1.55 M) was added thereto at -78 ℃, and the mixture was stirred at the same temperature for 4.5 hours to confirm the

loss of the starting material. 0.5 ml of acetic acid was added to the reaction solution to stop the reaction, and the temperature was elevated to a room temperature. The reaction solution was mixed with water, alkalinized with potassium carbonate, and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was concentrated under reduced pressure. The thus obtained residue was purified by a silica gel column chromatography to obtain 0.12 g of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(thiophen-2-yl)thiazol-2-yl]-2-methoxyisonicotinamide. The obtained compound was dissolved in 2 ml of EtOAc, 0.25 ml of 1M HCl-EtOAc solution was added thereto under ice cooling, and the mixture was stirred at room temperature overnight. The thus precipitated solid was filtered and dried to obtain 98 mg of N-[5-(4-cyclohexylpiperazin-1-yl)-4-(thiophen-2-yl)thiazol-2-yl]-2-methoxyisonicotinamide hydrochloride.

[0071]

Example 10

To a solution of 48 mg of 40% sodium hydride in 1 ml of ethyleneglycol, 100 mg of the compound of Example 66 was added at room temperature, the temperature was elevated to 50 ℃, and the mixture was stirred for 4 days. To the reaction solution, chloroform was added, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over sodium sulfate. After the evaporation of the solvent under reduced pressure, the obtained residue was purified by a silica gel column chromatography (chloroform-MeOH=200:1~20:1) and dissolved in 5 ml of EtOAc, 0.8 ml of 0.1M HCl-EtOAc solution was added thereto, and the mixture was stirred for

a while. Then, the solvent was evaporated under reduced pressure, and the residue was washed with diethylether to obtain 34 mg of 5-chloro-N-[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)thiazol-2-yl]-6-(2-hydroxyethoxy)nicotinamide hydrochloride.

[0072]

Example 11

To a solution of 200 mg of the compound of Example 66 in 2 ml of THF, 1 ml of 3-hydroxypropylamine were added, temperature was elevated to 50 ℃, and the mixture was stirred for 20 hours. Chloroform was added to the reaction solution, and the organic layer was washed with saturated aqueous NaHCO3 and brine, and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the obtained residue was purified by silica gel column chromatograph (elute: chloroform-MeOH=200:1-50:1), and dissolved in 10 ml of EtOAc. 7.8 ml of 0.1M hydrochloride-EtOAc were added thereto, and the mixture was stirred for a whole, and then the solvent was evaporated, and the residue was washed with diethylether to obtain 159 mg of 5-chloro-N-[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl) thiazol-2-yl]-6-(3-hydroxypropylamino)nicotinamide hydrochloride.

[0073]

Example 12

231 mg of the compound of Example 8 and 80 μl of benzaldehyde were dissolved in 9 ml of 1,2-dichloroethane-3 ml of acetic acid, 210 mg of sodium triacetoxyborohydride was added thereto at 0 ℃, and the mixture was

stirred at 0 ℃ for 30 minutes and at room temperature for 30 minutes. The reaction solution was alkalinized with saturated aqueous $NaHCO_3$ and 1M aqueous NaOH, and extracted with chloroform. The organic layer was dried over MgSO4, and the solvent was evaporated under reduced pressure. Then, to the obtained residue, 5 ml of acetic acid, total 160 μl of benzaldehyde and total 404 mg of sodium triacetoxyborohydride were added, and the mixture was stirred at 50 ℃ for 4 hours. The solvent was evaporated under reduced pressure, saturated aqueous $NaHCO_3$ was added to the obtained residue, and insoluble matter was collected by filtration. Chloroform was added thereto to dissolve it, and the solution was mixed with saturated aqueous $NaHCO_3$ and extracted with chloroform. The organic layer was dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The obtained residue was purified by a silica gel column chromatography (hexane-EtOAc = 4:1) and dissolved in EtOAc, and then 0.5 M HCl-EtOAc solution was added thereto, and the thus produced precipitate was collected by filtration to obtain 64 mg of N-[5-(4-benzylpiperazin-1-yl)-4-(4-chlorothiophen-2-yl)thiazol-2-yl]-2-methoxyisonicotinamide hydrochloride.

[0074]

Example 13

To a solution of 0.35 g of the compound of Example 51 in 5 ml of EtOAc, 4M HCl-EtOAc was added under ice cooling, and the mixture was stirred at room temperature for 1 hour. The thus precipitated solid was filtered to obtain 345 mg of 4-aminomethyl-N-[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)thiazol-2-yl]benzamide hydrochloride.

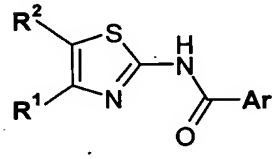
[0075]

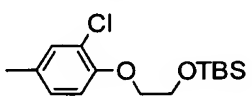
Example 14

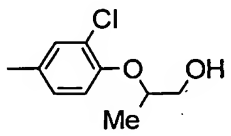
To a solution of 30 mg of the compound of Example 81 in 1 ml of MeOH, 0.12 ml of 1M NaOH aq. was added at room temperature, and the mixture was stirred for 24 hours. After the solvent was evaporated under reduced pressure, the obtained residue was dissolved in 5 ml of EtOAc, 0.2 ml of 1M HCl was added thereto, and the mixture was stirred for a while. Then, the solvent was evaporated under reduced pressure and washed with diethylether to obtain 20 mg of 5-chloro-N-[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperzain-1-yl)thiazol-2-yl]-6-(4-carboxypiperidin-1-yl)nicotinamide

[0076]

[Table 5]



Ex (Salt)	R^1, R^2, Ar	Data
1 (HCl)	R^1 : 5-Cl-2-The R^2 : 4-cHex-1-pipa Ar : 2-MeO-4-Py	MS;518.
2 (HCl)	R^1 : 5-Cl-2-The R^2 : 4-nPr-1-pipe Ar : 2-MeO-4-Py	NMR;0.90(3H,t,J=6.8Hz),1.22-1.50(7H,m),1.72-1.84(2H,m),2.60-2.72(2H,m),3.04-3.14(2H,m),3.92(3H,s),7.10(1H,d,J=3.9Hz),7.39(1H,d,J=3.9Hz),7.43(1H,s),7.53(1H,d,J=5.4Hz),8.36(1H,d,J=5.4Hz),12.81(1H,br). MS;477.
3	R^1 : 4-Cl-2-The R^2 : 4-cHex-1-pipa Ar : 	MS;695.

4 (HCl)	R^1 : 4-Cl-2-The R^2 : 4-cHex-1-pipa Ar : 5-Cl-6-HO-3-Py	MS;538.
5 (TFA)	R^1 : 4-Cl-2-The R^2 : 4-cHex-1-pipa Ar : 	NMR;1.07-1.19(1H,m),1.29(3H, d ,J=6.4Hz),1.26-1.48(4H,m),1.60-1.68(1H,m),1.82-1.92(2H,m),2.08-2.20(2H,m),3.02-3.16(2H,m),3.26-3.43(5H,m),3.50-3.70(4H,m),4.64-4.74(1H,m),4.96(1H,brs),7.38(1H,d,J=8.6Hz),7.51(1H,d,J=1.6Hz),7.57(1H,d,J=1.6Hz),8.06(1H,dd,J=2.2,8.6Hz),8.23(1H,d,J=2.2Hz),9.56(1H,brs),12.63(1H,brs). MS;595.
6 (HCl)	R^1 : 4-Cl-2-The R^2 : 4-cHex-1-pipa Ar : 3-F-4-HO-Ph	NMR;1.05-1.20(1H,m),1.21-1.36(2H,m),1.38-1.55(2H,m),1.58-1.68(1H,m),1.82-1.91(2H,m),2.14-2.25(2H,m),3.20-3.40(7H,m),3.55-3.65(2H,m),7.11(1H,dd,J=8.3,8.8Hz),7.49(1H,s),7.56(1H,s),7.83(1H,dd,J=1.4,8.3Hz),8.21(1H,dd,J=1.4,12.6Hz),10.95(1H,brs),12.50(1H,brs). MS;521.
7 (HCl)	R^1 : 4-Cl-2-The R^2 : 4-cHex-1-pipa Ar : 3-Cl-4-HO$(CH_2)_2$O-Ph	NMR;1.06-1.20(1H,m),1.22-1.36(2H,m),1.43-1.56(2H,m),1.59-1.68(1H,m),1.80-1.92(2H,m),2.17-2.27(2H,m),3.20-3.44(7H,m),3.54-3.63(2H,m),3.78(2H,t,J=4.9Hz),4.21(2H,t,J=4.9Hz),7.33(1H,d,J=8.8Hz),7.50(1H,d,J=1.5Hz),7.57(1H,d,J=1.5Hz),8.08(1H,dd,J=2.0,8.8Hz),8.24(1H,d,J=2.0Hz),10.89(1H,brs),12.61(1H,brs). MS;581.

[0077]

[Table 6]

Ex (Salt)	R^1, R^2, Ar	Data
8 (AcOH)	R^1 : 4-Cl-2-The R^2 : 1-pipa Ar : 2-MeO-4-Py	MS;436.
9 (HCl)	R^1 : 2-The R^2 : 4-cHex-1-pipa Ar : 2-MeO-4-Py	MS;484.
10 (HCl)	R^1 : 4-Cl-2-The R^2 : 4-cHex-1-pipa Ar : 5-Cl-6-HO$(CH_2)_2$O-3-Py	NMR;1.09-1.20(1H,m),1.22-1.36(2H,m),1.42-1.54(2H,m),1.60-1.68(1H,m),1.81-1.91(2H,m),2.14-2.24(2H,m),3.26-3.35(7H,m),3.55-3.65(2H,m),3.77(2H,t,J=4.9Hz),4.48(2H,t,J=4.9Hz),7.50(1H,brs),7.58(1H,brs),8.54(1H,d,J=1.9Hz),8.81(1H,d,J=1.9Hz),10.76(1H,brs),12.78(1H,brs). MS;582.
11 (HCl)	R^1 : 4-Cl-2-The R^2 : 4-cHex-1-pipa Ar : 5-Cl-6-HO$(CH_2)_3$NH-3-Py	NMR;1.05-1.20(1H,m),1.22-1.36(2H,m),1.42-1.54(2H,m),1.60-1.68(1H,m),1.70-1.77(2H,m),1.82-1.92(2H,m),2.15-2.25(2H,m),3.20-3.40(7H,m),3.45-3.65(4H,m),3.49(2H,t,J=6.3Hz),7.39(1H,brs),7.48(1H,d,J=1.5Hz),7.56(1H,d,J=1.5Hz),8.27(1H,d,J=2.0Hz),8.74(1H,d,J=2.0Hz),10.98(1H,brs),12.45(1H,s). MS;595.

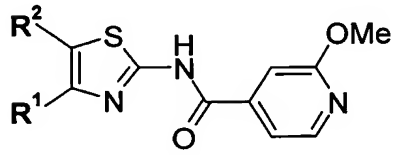
12 (HCl)	R^1 : 4-Cl-2-The R^2 : 4-Bn-1-pipa Ar : 2-MeO-4-Py	MS;526.
13 (HCl)	R^1 : 4-Cl-2-The R^2 : 4-cHex-1-pipa Ar : 4-H_2NCH_2-Ph	MS;516.
14 (HCl)	R^1 : 4-Cl-2-The R^2 : 4-cHex-1-pipa Ar : 5-Cl-6-(4-HO_2C-1-pipe)-3-Py	NMR;1.06-1.20(1H,m),1.22-1.36(2H,m),1.40-1.55(2H,m),1.58-1.70(3H,m),1.78-2.00(4H,m),2.15-2.25(2H,m),2.50-2.58(1H,m),2.98-3.09(2H,m),3.23-3.40(7H,m),3.54-3.66(2H,m),3.93-4.02(2H,m),7.48(1H,d,J=1.5Hz),7.57(1H,d,J=1.5Hz),8.40(1H,d,J=1.9Hz),8.83(1H,d,J=1.9Hz),10.98(1H,brs),12.28(1H,brs),12.68(1H,s). MS;649.

[0078]

Compounds of Examples 15-89 as shown in Tables 7-18 were synthesized in the same manner as described in the Examples, employing each corresponding starting material.

[0079]

[Table 7]

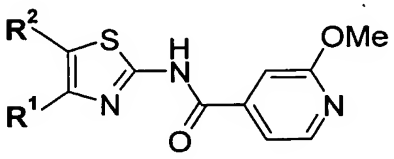


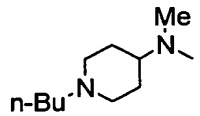
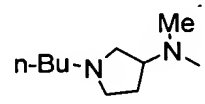
Ex (Salt)	Syn	R^1,R^2	Data
15 (HCl)	1	R^1 : 5-Me-2-Fur R^2 : 4-cHex-1-pipa	MS;482.
16 (HCl)	3	R^1 : 3-Cl-2-The R^2 : 4-cHex-1-pipa	MS;518.
17 (HCl)	2	R^1 : 5-Cl-3-The R^2 : 4-cHex-1-pipa	MS;518.
18 (HCl)	3	R^1 : 4-Cl-2-The R^2 : 4-cHex-1-pipa	NMR;1.08-1.20(1H,m),1.21-1.34(2H,m),1.40-1.53(2H,m),1.60-1.68(1H,m),1.82-1.89(2H,m),2.14-2.24(2H,m),3.22-3.45(7H,m),3.55-3.65(2H,m),3.95(3H,s),7.44(1H,s),7.50(1H,s),7.54(1H,d,J=4.9Hz),7.56(1H,s),8.37(1H,d,J=4.9Hz),10.61(1H,brs),12.95(1H,brs). MS;518.
19 (HCl)	1	R^1 : 5-Br-2-The R^2 : 4-cHex-1-pipa	MS;562,564.
20 (HCl)	3	R^1 : 5-F-2-The R^2 : 4-cHex-1-pipa	MS;502.

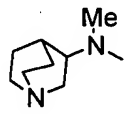
21 (HCl)	3	R^1 : 4-Br-2-The R^2 : 4-cHex-1-pipa	NMR;1.06-1.21(1H,m),1.23-1.36(2H,m),1.42-1.56(2H,m),1.58-1.70(1H,m),1.80-1.91(2H,m),2.15-2.26(2H,m),3.20-3.43(5H,m),3.55-3.67(4H,m),3.92(3H,s),7.44(1H,s),7.52(1H,d,J=1.5Hz),7.54(1H,dd,J=1.5,5.4Hz),7.67(1H,d,J=1.5Hz),8.37(1H,d,J=5.4Hz),11.09(1H,brs),12.93(1H,brs). MS;562,564.
22 (HCl)	1	R^1 : 5-Me-2-The R^2 : 4-cHex-1-pipa	MS;498.
23 (HCl)	3	R^1 : 4-Me-2-The R^2 : 4-cHex-1-pipa	MS;498.
24 (HCl)	3	R^1 : 3-F-2-The R^2 : 4-cHex-1-pipa	MS;502.

[0080]

[Table 8]

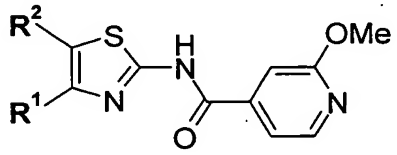


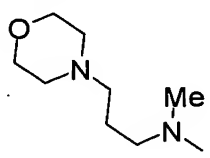
Ex (Salt)	Syn	R^1,R^2	Data
25 (HCl)	3	R^1 : 4-Cl-2-The R^2 : 4-nPr-1-pipe	NMR;0.90(3H,t,J=6.8Hz),1.22-1.49(7H,m),1.75-1.85(2H,m),2.63-2.71(2H,m),3.06-3.16(2H,m),3.92(3H,s),7.42(1H,d,J=2.0Hz),7.43(1H,s),7.51(1H,d,J=2.0Hz),7.54(1H,d,J=5.4Hz),8.36(1H,d,J=5.4Hz),12.80(1H,brs). MS;477.
26 (HCl)	3	R^1 : 4-Cl-2-The R^2 : 	MS;520.
27 (HCl)	3	R^1 : 4-Cl-2-The R^2 : 4-allylO_2C-1-pipa	MS;519.
28 (HCl)	3	R^1 : 4-Cl-2-The R^2 : 3-(4-nPr-1-pipe)-azetidin-1-yl	MS;532.
29 (HCl)	3	R^1 : 4-Cl-2-The R^2 : 4-Mor-1-pipe	MS;520.
30 (HCl)	3	R^1 : 4-Cl-2-The R^2 : 	MS;506.

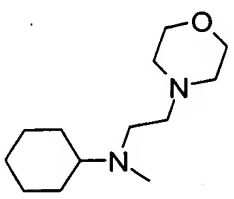
31 (HCl)	3	R^1 : 4-Cl-2-The R^2 : 	MS;490.
32 (HCl)	3	R^1 : 4-F-5-Cl-2-The R^2 : 4-cHex-1-pipa	NMR;1.08-1.20(1H,m),1.21-1.36(2H,m),1.40-1.55(2H,m),1.58-1.68(1H,m),1.82-1.92(2H,m),2.14-2.25(2H,m),3.22-3.45(7H,m),3.56-3.65(2H,m),3.92(3H,s),7.44(1H,s),7.46(1H,s),7.54(1H,d,J=5.4Hz),8.37(1H,d,J=5.4Hz),10.63(1H,brs),13.02(1H,brs). MS;536.

[0081]

[Table 9]

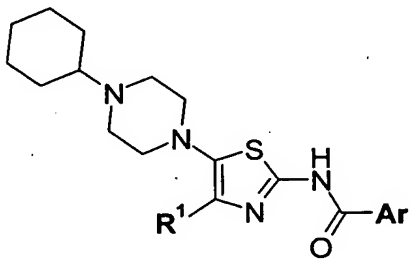


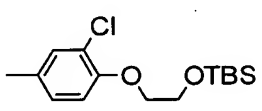
Ex (Salt)	Syn	R^1,R^2	Data
33 (HCl)	3	R^1 : 4-F-2-The R^2 : 4-cHex-1-pipa	NMR;1.08-1.20(1H,m),1.21-1.36(2H,m),1.38-1.55(2H,m),1.60-1.70(1H,m),1.82-1.92(2H,m),2.14-2.25(2H,m),3.20-3.45(7H,m),3.55-3.65(2H,m),3.92(3H,s),7.18(1H,brs),7.45(1H,brs),7.48(1H,s),7.54(1H,d,J=5.4Hz),8.37(1H,d,J=5.4Hz),10.30(1H,brs),12.97(1H,brs). MS;502.
34 (HCl)	3	R^1 : 4-Cl-2-The R^2 : 4-nPr-1-pipa	NMR; 0.95(3H,t,J=7.3Hz),1.72-1.84(2H,m),3.10-3.19(2H,m),3.22-3.35(6H,m),3.58-3.64(2H,m),3.92(3H,s),7.44(1H,s),7.51(1H,d,J=1.5Hz),7.54(1H,dd,J=1.3Hz,J=5.2Hz),7.59(1H,d,J=1.4Hz),8.37(1H,d,J=4.8Hz),11.01(1H,brs),12.95(1H,s). MS;478.
35 (HCl)	12	R^1 : 4-Cl-2-The R^2 : 4-(2-The-CH_2)-1-pipa	MS;532.
36 (HCl)	12	R^1 : 4-Cl-2-The R^2 : 4-(2-Py-CH_2)-1-pipa	MS;527.
37 (HCl)	12	R^1 : 4-Cl-2-The R^2 : 4-(4-Et-cHex)-1-pipa	MS;546.
38 (HCl)	3	R^1 : 4-Cl-2-The R^2 : 	MS;508.

39 (HCl)	3	R^1 : 4-Cl-2-The R^2 : 	MS;562.

[0082]

[Table 10]

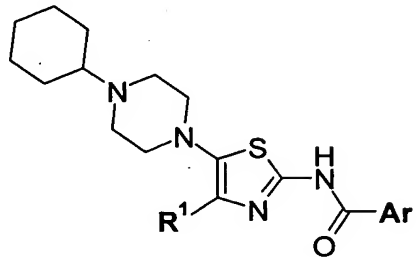


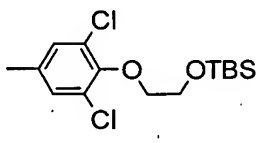
Ex (Salt)	Syn	R^1,Ar	Data
40 (HCl)	2	R^1 : 5-Cl-2-The Ar : 5-MeO-3-Py	MS;518.
41	3	R^1 : 5-Cl-2-The Ar : 3-F-4-$MeOCH_2O$-Ph	NMR($CDCl_3$);1.10-1.35(5H,m),1.62-1.70(1H,m),1.80-2.02(4H,m), 2.29-2.41(1H,m),2.77-2.83(4H,m),3.00-3.06(4H,m),3.52(3H,s),5.27(2H,s),6.73(1H,d,J=4.0Hz),7.16-7.21(2H,m),7.54-7.59(2H,m).
42 (HCl)	2	R^1 : 5-Cl-2-The Ar : 2-Cl-6-Me-4-Py	MS;536.
43 (HCl)	2	R^1 : 5-Cl-2-The Ar : 2-MeO-6-Me-4-Py	MS;532.
44 (HCl)	2	R^1 : 5-Cl-2-The Ar : 2-Cl-6-MeO-4-Py	MS;552.
45 (HCl)	2	R^1 : 5-Cl-2-The Ar : 3-F-4-$MeO(CH_2)_2O$-Ph	MS;579.
46 (HCl)	2	R^1 : 5-Cl-2-The Ar : 2,6-diF-4-$MeO(CH_2)_2O$-Ph	MS;597.
47 (HCl)	2	R^1 : 5-Cl-2-The Ar : 3-Cl-4-$MeO(CH_2)_2O$-Ph	MS;595.
48	3	R^1 : 5-Cl-2-The Ar : 	MS;695.

49 (HCl)	2	R^1 : 5-Cl-2-The Ar : quinolin-6-yl	NMR;1.03-1.20(1H,m),1.21-1.36(2H,m),1.40-1.55(2H,m),1.60-1.68(1H,m),1.82-1.91(2H,m),2.14-2.24(2H,m),3.22-3.40(7H,m),3.55-3.65(2H,m),7.14(1H,d,J=4.4Hz),7.50(1H,d,J=4.4Hz),7.72(1H,dd,J=4.4,8.8Hz),8.18(1H,d,J=8.8Hz),8.37(1H,dd,J=1.9,8.8Hz), 8.61(1H,d,J=8.8Hz),8.87(1H,d,J=1.9Hz),9.09(1H,d,J=4.4Hz),10.71(1H,brs),12.96(1H,brs). MS;538.

[0083]

[Table 11]

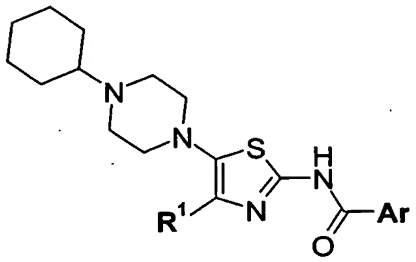


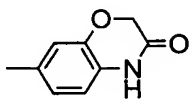
Ex (Salt)	Syn	R^1,Ar	Data
50 (HCl)	2	R^1 : 5-Cl-2-The Ar : 2,6-diMeO-pyrimidin-4-yl	MS;549.
51	3	R^1 : 4-Cl-2-The Ar : 4-$tBuO_2CHNCH_2$-Ph	MS;616.
52	3	R^1 : 4-Cl-2-The Ar : 3-F-4-$MeOCH_2O$-Ph	MS;565.
53	3	R^1 : 4-Cl-2-The Ar : 3-Cl-4-$MeOCH_2O$-Ph	MS;581.
54 (HCl)	3	R^1 : 4-Cl-2-The Ar : 3-Cl-4-$MeO(CH_2)_2O$-Ph	NMR;1.06-1.20(1H,m),1.22-1.36(2H,m),1.44-1.56(2H,m),1.58-1.68(1H,m),1.80-1.92(2H,m),2.15-2.26(2H,m),3.17-3.47(7H,m),3.35(3H,s),3.56-3.63(2H,m),3.73(2H,t,J=3.9Hz),4.31(2H,t,J=3.9Hz),7.33(1H,d,J=8.8Hz),7.49(1H,d,J=0.9Hz),7.56(1H,d,J=0.9Hz),8.08(1H,dd,J=1.9,8.8Hz),8.24(1H,d,J=1.9Hz),11.31(1H,brs),12.61(1H,brs). MS;595.
55	3	R^1 : 4-Cl-2-The Ar : 	MS;729.

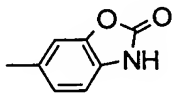
56 (HCl)	3	R^1 : 4-Cl-2-The Ar : isoquinolin-6-yl	NMR;1.03-1.20(1H,m),1.21-1.36(2H,m),1.40-1.55(2H,m),1.60-1.68(1H,m),1.82-1.91(2H,m),2.18-2.28(2H,m),3.20-3.43(7H,m),3.52-3.65(2H,m),7.52(1H,s),7.59(1H,s),8.33-8.40(2H,m),8.50(1H,d,J=8.8Hz),8.73(1H,d,J=5.8Hz), 8.90(1H,s),9.78(1H,s),11.20(1H,brs),13.12(1H,brs). MS;538.

[0084]

[Table 12]

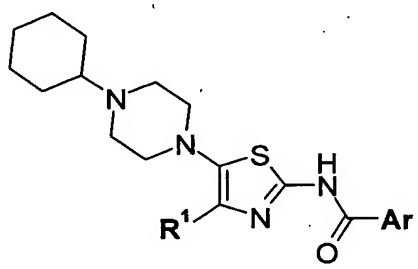


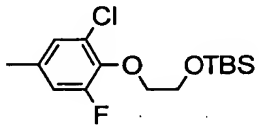
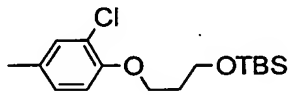
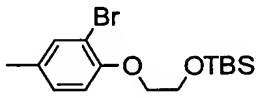
Ex (Salt)	Syn	R^1,Ar	Data
57 (HCl)	3	R^1 : 4-Cl-2-The Ar : quinolin-6-yl	NMR;1.03-1.20(1H,m),1.21-1.36(2H,m),1.38-1.55(2H,m),1.60-1.68(1H,m),1.82-1.91(2H,m),2.18-2.25(2H,m),3.22-3.40(7H,m),3.55-3.65(2H,m),7.52(1H,s),7.58(1H,s),7.76(1H,dd,J=4.2,8.3Hz),8.21(1H,d,J=8.8Hz),8.40(1H,dd,J=1.5,8.8Hz), 8.67(1H,d,J=8.3Hz),8.89(1H,d,J=1.5Hz),9.11(1H,d,J=4.2Hz),11.05(1H,brs),12.96(1H,brs). MS;538.
58 (HCl)	3	R^1 : 4-Cl-2-The Ar : 2-H_2NOC-quinolin-6-yl	NMR;1.05-1.20(1H,m),1.21-1.36(2H,m),1.41-1.56(2H,m),1.60-1.68(1H,m),1.82-1.92(2H,m),2.18-2.25(2H,m),3.22-3.40(7H,m),3.55-3.65(2H,m),7.52(1H,s),7.58(1H,s),7.88(1H,s),8.21-8.28(2H,m),8.36(1H,s),8.41(1H,dd,J=1.1,8.8Hz), 8.71(1H,d,J=8.8Hz),8.90(1H,d,J=1.1Hz),10.92(1H,brs),12.98(1H,brs). MS;581.
59 (HCl)	3	R^1 : 4-Cl-2-The Ar : 	NMR;1.05-1.20(1H,m),1.22-1.36(2H,m),1.41-1.56(2H,m),1.58-1.67(1H,m),1.80-1.92(2H,m),2.16-2.25(2H,m),3.20-3.45(7H,m),3.53-3.65(2H,m),4.67(2H,s),7.03(1H,d,J=8.3Hz),7.49(1H,s),7.56(1H,s),7.73-7.77(2H,m),11.10(1H,s),11.13(1H,brs),12.54(1H,brs). MS;558.

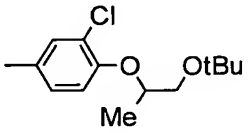
60 (HCl)	3	R^1 : 4-Cl-2-The Ar : 	NMR;1.07-1.20(1H,m),1.22-1.36(2H,m),1.41-1.55(2H,m),1.59-1.68(1H,m),1.82-1.92(2H,m),2.14-2.24(2H,m),3.27-3.35(7H,m),3.55-3.65(2H,m),7.24(1H,d,J=8.3Hz),7.50(1H,d,J=1.5Hz),7.57(1H,d,J=1.5Hz),7.97(1H,dd,J=1.5,8.3Hz),8.06(1H,s),10.74(1H,brs),12.13(1H,s),12.63(1H,brs). MS;544.

[0085]

[Table 13]

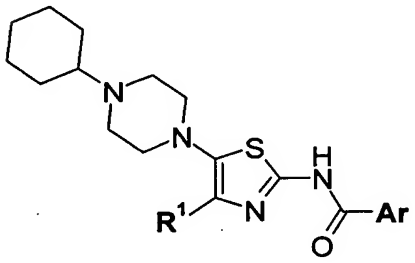


Ex (Salt)	Syn	R^1,Ar	Data
61	3	R^1 : 4-Cl-2-The Ar : 	MS;713.
62	3	R^1 : 4-Cl-2-The Ar : 	MS;709.
63	3	R^1 : 4-Cl-2-The Ar : 	MS;739,741.
64 (HCl)	3	R^1 : 4-Cl-2-The Ar : 2-EtO-4-Py	MS;532.
65 (HCl)	3	R^1 : 4-Cl-2-The Ar : 5-Cl-6-MeO-3-Py	MS;552.
66	3	R^1 : 4-Cl-2-The Ar : 5,6-diCl-3-Py	MS;556.

67 (HCl)	3	R^1 : 4-Cl-2-The Ar : 	MS;651.
68 (HCl)	11	R^1 : 4-Cl-2-The Ar : 5-Cl-6-HO$(CH_2)_2$ N(Me)-3-Py	NMR;1.06-1.20(1H,m),1.22-1.36(2H,m),1.42-1.57(2H,m),1.59-1.68(1H,m),1.80-1.92(2H,m),2.16-2.27(2H,m),3.18(3H,s),3.20-3.64(13H,m),7.48(1H,d,J=1.5Hz),7.56(1H,d,J=1.5Hz),8.33(1H,d,J=2.0Hz),8.77(1H,d,J=2.0Hz),11.27(1H,brs),12.58(1H,brs). MS;595.

[0086]

[Table 14]

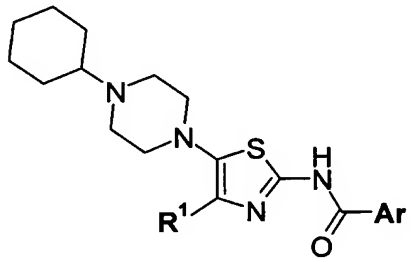


Ex (Salt)	Syn	R^1,Ar	Data
69 (HCl)	11	R^1 : 4-Cl-2-The Ar : 5-Cl-6-HO$(CH_2)_2$NH -3-Py	NMR;1.06-1.21(1H,m),1.22-1.36(2H,m),1.39-1.53(2H,m),1.58-1.68(1H,m),1.80-1.92(2H,m),2.13-2.24(2H,m),3.18-3.38(7H,m),3.50-3.64(6H,m),7.20(1H,brs),7.49(1H,d,J=1.4Hz),7.56(1H,d,J=1.4Hz),8.28(1H,d,J=2.0Hz),8.74(1H,d,J=2.0Hz),10.35(1H,brs),12.47(1H,brs). MS;581.
70 (HCl)	6	R^1 : 5-Cl-2-The Ar : 3-F-4-HO-Ph	MS;521.
71 (HCl)	6	R^1 : 4-Cl-2-The Ar : 3-Cl-4-HO-Ph	NMR;1.06-1.20(1H,m),1.21-1.36(2H,m),1.42-1.56(2H,m),1.59-1.68(1H,m),1.81-1.91(2H,m),2.16-2.26(2H,m),3.20-3.45(7H,m),3.54-3.63(2H,m),7.17(1H,d,J=8.8Hz),7.49(1H,d,J=1.4Hz),7.56(1H,d,J=1.4Hz),7.94(1H,dd,J=2.4,8.8Hz),8.19(1H,d,J=2.4Hz),11.26(1H,brs),12.51(1H,brs). MS;537.

72 (HCl)	7	R^1 : 5-Cl-2-The Ar : 3-Cl- 4-HO$(CH_2)_2$O-Ph	NMR;1.07-1.20(1H,m),1.22-1.36(2H,m),1.42-1.55(2H,m),1.60-1.68(1H,m),1.81-1.91(2H,m),2.16-2.26(2H,m),3.20-3.29(7H,m),3.56-3.65(2H.m),3.78(2H,t,J=4.9Hz),4.21(2H,t,J=4.9Hz),7.12(1H,d,J=3.9Hz),7.33(1H,d,J=8.8Hz),7.47(1H,d,J=3.9Hz),8.08(1H,dd,J=8.8,2.0Hz),8.23(1H,d,J=2.0Hz),10.93(1H,brs),12.63(1H,brs). MS;581.
73 (HCl)	7	R^1 : 4-Cl-2-The Ar : 3,5-diCl- 4-HO$(CH_2)_2$O-Ph	NMR;1.07-1.20(1H,m),1.22-1.36(2H,m),1.44-1.56(2H,m),1.60-1.68(1H,m),1.83-1.91(2H,m),2.17-2.26(2H,m),3.20-3.42(7H,m),3.56-3.63(2H,m),3.78(2H,t,J=4.9Hz),4.13(2H,t,J=4.9Hz),7.49(1H,s),7.57(1H,s),8.21(2H,s),11.18(1H,brs),12.79(1H,brs). MS;615.

[0087]

[Table 15]

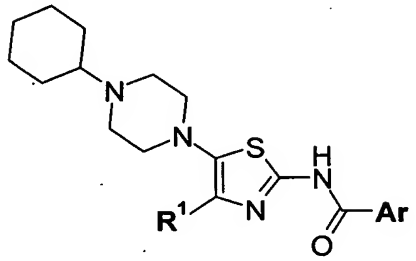


Ex (Salt)	Syn	R^1,Ar	Data
74 (HCl)	7	R^1 : 4-Cl-2-The Ar : 3-Cl-5-F- 4-HO$(CH_2)_2$O-Ph	NMR;1.07-1.20(1H,m),1.21-1.36(2H,m),1.41-1.54(2H,m),1.58-1.68(1H,m),1.80-1.92(2H,m),2.14-2.25(2H,m),3.25-3.37(7H,m),3.56-3.64(2H,m),3.73(2H,t,J=4.9Hz),4.24(2H,t,J=4.9Hz),7.50(1H,d,J=1.0Hz),7.58(1H,d,J=1.0Hz),8.01(1H,dd,J=2.0,11.7Hz),8.11(1H,brs),10.77(1H,brs),12.77(1H,brs). MS;599.
75 (HCl)	7	R^1 : 4-Cl-2-The Ar : 3-Cl- 4-HO$(CH_2)_3$O-Ph	NMR;1.08-1.20(1H,m),1.22-1.36(2H,m),1.41-1.55(2H,m),1.58-1.68(1H,m),1.82-1.90(2H,m),1.92(2H,t,J=6.3Hz),2.19-2.22(2H,m),3.21-3.37(7H,m),3.55-3.63(4H,m),4.25(2H,t,J=6.3Hz),7.32(1H,d,J=8.8Hz),7.50(1H,s),7.57(1H,s),8.09(1H,dd,J=2.0,8.8Hz),8.24(1H,d,J=2.0Hz),10.83(1H,brs),12.62(1H,brs). MS;595.

76 (HCl)	7	**R^1** : 4-Cl-2-The **Ar** : 3-Br-4-$HO(CH_2)_2O$-Ph	NMR;1.07-1.20(1H,m),1.22-1.36(2H,m),1.42-1.56(2H,m),1.60-1.67(1H,m),1.81-1.90(2H,m),2.18-2.25(2H,m),3.17-3.43(7H,m),3.55-3.65(2H,m),3.78(2H,t,J=4.9Hz),4.20(2H,t,J=4.9Hz),7.29(1H,d,J=8.8Hz),7.49(1H,d,J=1.5Hz),7.56(1H,d,J=1.5Hz),8.12(1H,dd,J=2.4,8.8Hz),8.39(1H,d,J=2.4Hz),11.19(1H,brs),12.61(1H,brs). MS;625,627.
77 (HCl)	12	**R^1** : 4-Cl-2-The **Ar** : 4-Me_2NCH_2-Ph	MS;544.

[0088]

[Table 16]

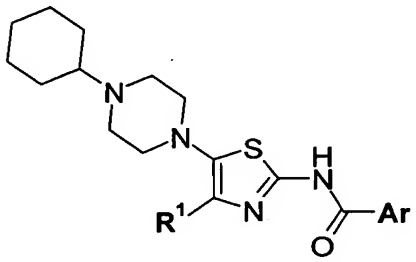


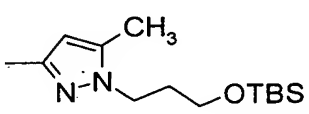
Ex (Salt)	Syn	R^1,Ar	Data
78 (HCl)	11	**R^1** : 4-Cl-2-The **Ar** : 5-Cl-6-$MeO(CH_2)_2HN$-3-Py	NMR;1.05-1.20(1H,m),1.22-1.36(2H,m),1.42-1.56(2H,m),1.58-1.68(1H,m),1.80-1.93(2H,m),2.17-2.25(2H,m),3.22-3.45(7H,m),3.28(3H,s),3.51(2H,t,J=5.8Hz),3.55-3.67(4H,m),7.30(1H,brs),7.49(1H,brs),7.56(1H,brs),8.29(1H,d,J=1.9Hz),8.74(1H,d,J=1.9Hz),11.12(1H,brs),12.47(1H,brs). MS;595.
79 (HCl)	11	**R^1** : 4-Cl-2-The **Ar** : 5-Cl-6-(4-HO-1-pipe)-3-Py	NMR;1.07-1.20(1H,m),1.22-1.36(2H,m),1.41-1.56(4H,m),1.60-1.67(1H,m),1.80-1.92(4H,m),2.15-2.24(2H,m),3.13-3.37(9H,m),3.55-3.63(2H,m),3.68-3.76(1H,m),3.79-3.87(2H,m),7.49(1H,d,J=1.4Hz),7.57(1H,d,J=1.4Hz),8.38(1H,d,J=2.4Hz),8.82(1H,d,J=2.4Hz),10.92(1H,brs),12.66(1H,s). MS;621.
80 (HCl)	11	**R^1** : 4-Cl-2-The **Ar** : 5-Cl-6-(3-oxo-1-pipa)-3-Py	NMR;1.06-1.20(1H,m),1.22-1.36(2H,m),1.40-1.54(2H,m),1.58-1.69(1H,m),1.81-1.92(2H,m),2.13-2.24(2H,m),3.23-3.38(8H,m),3.57-3.63(3H,m),3.77(2H,t,J=5.4Hz),4.05(2H,brs),7.49(1H,d,J=1.5Hz),7.57(1H,d,J=1.5Hz),8.05(1H,brs),8.45(1H,d,J=1.9Hz),8.86(1H,d,J=1.9Hz),10.62(1H,brs),12.73(1H,s). MS;620.

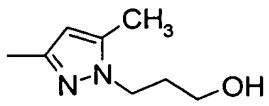
81 (HCl)	11	R^1 : 4-Cl-2-The Ar : 5-Cl -6-(4-EtO_2C-1-pipe) -3-Py	NMR;1.05-1.20(1H,m),1.20(3H,t,J=6.8Hz),1.22-1.36(2H,m),1.42-1.55(2H,m),1.58-1.75(3H,m),1.80-2.00(4H,m),2.16-2.25(2H,m),2.57-2.68(1H,m),3.00-3.08(2H,m),3.20-3.47(7H,m),3.53-3.65(2H,m),3.93-4.04(2H,m),4.08(2H,q,J=6.8Hz),7.49(1H,d,J=1.5Hz),7.56(1H,d,J=1.5Hz),8.40(1H,d,J=2.0Hz),8.84(1H,d,J=2.0Hz),11.17(1H,brs),12.67(1H,s). MS;677.

[0089]

[Table 17]

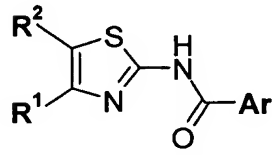


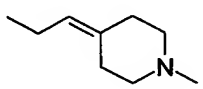
Ex (Salt)	Syn	R^1,Ar	Data
82 (HCl)	11	R^1 : 4-Cl-2-The Ar : 5-Cl -6-(H_2NOC-1-pipe) -3-Py	NMR;1.05-1.20(1H,m),1.22-1.36(2H,m),1.41-1.54(2H,m),1.58-1.74(3H,m),1.77-1.92(4H,m),2.16-2.24(2H,m),2.34-2.42(1H,m),2.95(2H,t,J=12.2Hz),3.25-3.36(7H,m),3.52-3.64(2H,m),4.07(2H,d,J=12.2Hz),6.80(1H,s),7.32(1H,s),7.49(1H,d,J=1.5Hz),7.57(1H,d,J=1.5Hz),8.40(1H,d,J=2.4Hz),8.83(1H,d,J=2.4Hz),10.73(1H,brs),12.67(1H,s). MS;648.
83 (HCl)	10	R^1 : 4-Cl-2-The Ar : 5-Cl-6-$HO(CH_2)_3O$ -3-Py	NMR;1.06-1.20(1H,m),1.22-1.36(2H,m),1.41-1.54(2H,m),1.60-1.68(1H,m),1.82-1.95(2H,m),1.92(2H,t,J=6.4Hz),2.15-2.24(2H,m),3.22-3.36(7H,m),3.55-3.63(2H,m),3.58(2H,t,J=6.4Hz),4.51(2H,t,J=6.4Hz),7.49(1H,d,J=1.5Hz),7.57(1H,d,J=1.5Hz),8.53(1H,d,J=2.0Hz),8.82(1H,d,J=2.0Hz),10.83(1H,brs),12.78(1H,s). MS;596.
84	3	R^1 : 4-Cl-2-The Ar : 	MS;663.

85 (HCl)	13	R^1 : 4-Cl-2-The Ar : 	MS;549.

[0090]

[Table 18]



Ex (Salt)	Syn	R^1, R^2, Ar	Data
86 (HCl)	2	R^1 : 5-Cl-2-The R^2 : 4-nPr-1-pipe Ar : quinolin-6-yl	NMR;0.90(3H,t,J=6.9Hz),1.25-1.50(7H,m),1.75-1.87(2H,m),2.65-2.75(2H,m),3.04-3.18(2H,m),7.11(1H,d,J=3.9Hz),7.41(1H,d,J=3.9Hz),8.01(1H,dd,J=3.9,8.3Hz),8.41(1H,d,J=8.8Hz),8.55(1H,d,J=8.8Hz),8.96-9.07(2H,m),9.30(1H,d,J=3.9Hz),12.96(1H,brs). MS;497.
87 (HCl)	2	R^1 : 5-Cl-2-The R^2 :  Ar : quinolin-6-yl	MS;495.
88 (HCl)	7	R^1 : 4-Cl-2-The R^2 : 4-nPr-1-pipa Ar : 3-Cl-4-HO(CH_2)$_2$O-Ph	NMR;0.95(3H,t,J=7.3Hz),1.71-1.82(2H,m),3.11-3.36(8H,m),3.60(2H,d,J=10.3Hz),3.78(2H,t,J=5.2Hz),4.21(2H,t,J=4.9Hz),7.33(1H,d,J=8.8Hz),7.50(1H,d,J=1.9Hz),7.58(1H,d,J=2.0Hz),8.08(1H,dd,J=2.0Hz,J=8.8Hz),8.24(1H,d,J=2.0Hz),10.73(1H,brs),12.62(1H,s). MS;541.
89 (HCl)	3	R^1 : 4-Cl-2-The R^2 : Mor Ar : quinolin-6-yl	NMR;2.95(4H,brs),3.83(4H,brs),7.50(1H,d,J=1.5Hz),7.55(1H,d,J=1.5Hz),7.82(1H,dd,J=4.4Hz,J=8.3Hz),8.24(1H,d,J=8.8Hz),8.43(1H,d,J=8.8Hz),8.75(1H,d,J=7.8Hz),8.92(1H,s),9.16(1H,d,J=4.4Hz),12.92(1H,brs). MS;457.

[0091]

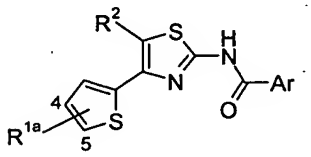
The structures of the compounds of the invention are shown in Tables 19-36. These compounds can be easily synthesized by the above

described production method, methods described in the Examples and modified methods thereof.

No in the Tables indicate compound number.

[0092]

[Table 19]

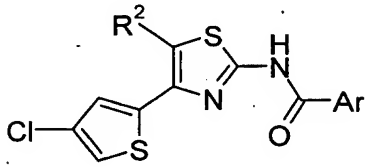


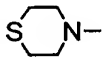
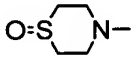
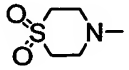
No	R^{1a}	R^2	Ar
A1	5-CF_3	4-cHex-1-pipa	2-MeO-4-Py
A2			quinolin-6-yl
A3			3-Cl-4-HO$(CH_2)_2$O-Ph
A4			5-Cl-6-HO$(CH_2)_3$NH-3-Py
A5			3-Cl-4-HO-Ph
A6	4-Br		2-MeO-4-Py
A7			quinolin-6-yl
A8			3-Cl-4-HO$(CH_2)_2$O-Ph
A9			5-Cl-6-HO$(CH_2)_3$NH-3-Py
A10			3-Cl-4-HO-Ph
A11	4-F		quinolin-6-yl
A12			3-Cl-4-HO$(CH_2)_2$O-Ph
A13			5-Cl-6-HO$(CH_2)_3$NH-3-Py
A14			3-Cl-4-HO-Ph
A15	4-CF_3		2-MeO-4-Py
A16			quinolin-6-yl
A17			3-Cl-4-HO$(CH_2)_2$O-Ph
A18			5-Cl-6-HO$(CH_2)_3$NH-3-Py
A19			3-Cl-4-HO-Ph
A20	4-F-5-Cl		quinolin-6-yl
A21			3-Cl-4-HO$(CH_2)_2$O-Ph
A22			5-Cl-6-HO$(CH_2)_3$NH-3-Py
A23			3-Cl-4-HO-Ph
A24	4,5-diCl		2-MeO-4-Py
A25			quinolin-6-yl
A26			3-Cl-4-HO$(CH_2)_2$O-Ph
A27			5-Cl-6-HO$(CH_2)_3$NH-3-Py
A28			3-Cl-4-HO-Ph
A29			quinolin-6-yl
A30			5-Cl-6-HO(CH2)3NH-3-Py
A31			3-Cl-4-HO-Ph
A32			2-MeO-4-Py
A33			quinolin-6-yl
A34			3-Cl-4-HO(CH2)2O-Ph
A35			5-Cl-6-HO(CH2)3NH-3-Py

A36			3-Cl-4-HO-Ph
A37			2-MeO-4-Py
A38			quinolin-6-yl
A39			3-Cl-4-HO(CH2)2O-Ph
A40			5-Cl-6-HO(CH2)3NH-3-Py
A41			3-Cl-4-HO-Ph

[0093]

[Table 20]

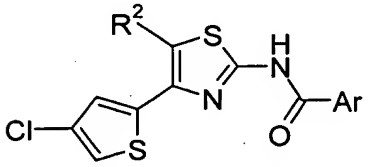


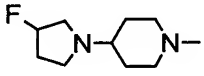
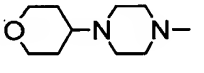
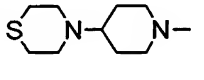
No	R^2	Ar
B1	Mor	2-MeO-4-Py
B2		quinolin-6-yl
B3		3-Cl-4-HO$(CH_2)_2$O-Ph
B4		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B5		3-Cl-4-HO-Ph
B6		2-MeO-4-Py
B7		quinolin-6-yl
B8		3-Cl-4-HO$(CH_2)_2$O-Ph
B9		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B10		3-Cl-4-HO-Ph
B11		2-MeO-4-Py
B12		qinolin-6-yl
B13		3-Cl-4-HO$(CH_2)_2$O-Ph
B14		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B15		3-Cl-4-HO-Ph
B16		2-MeO-4-Py
B17		quinolin-6-yl
B18		3-Cl-4-HO$(CH_2)_2$O-Ph
B19		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B20		3-Cl-4-HO-Ph
B21	4-nBu-1-pipa	2-MeO-4-Py
B22		quinolin-6-yl
B23		3-Cl-4-HO$(CH_2)_2$O-Ph
B24		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B25		3-Cl-4-HO-Ph
B26	4-(3-Pentyl)-1-pipa	2-MeO-4-Py
B27		quinolin-6-yl
B28		3-Cl-4-HO(CH2)2O-Ph
B29		5-Cl-6-HO(CH2)3NH-3-Py
B30		3-Cl-4-HO-Ph
B31	4-Pr-3,5-diMe-1-pipa	2-MeO-4-Py
B32		quinolin-6-yl
B33		3-Cl-4-HO(CH2)2O-Ph
B34		5-Cl-6-HO(CH2)3NH-3-Py
B35		3-Cl-4-HO-Ph

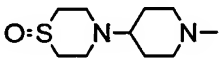
B36	4-cPent-1-pipa	2-MeO-4-Py
B37		quinolin-6-yl
B38		3-Cl-4-HO(CH2)2O-Ph
B39		5-Cl-6-HO(CH2)3NH-3-Py
B40		3-Cl-4-HO-Ph

[0094]

[Table 21]

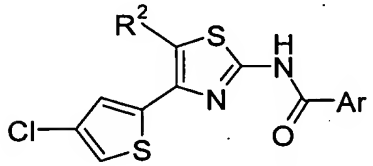


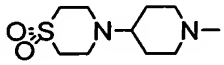
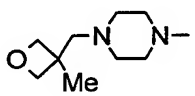
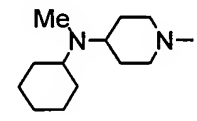
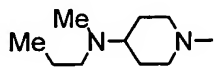
No	R^2	Ar
B41	4-cHept-1-pipa	2-MeO-4-Py
B42		qionolin-6-yl
B43		3-Cl-4-HO$(CH_2)_2$O-Ph
B44		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B45		3-Cl-4-HO-Ph
B46	4-nPr-1-pipe	quinolin-6-yl
B47		3-Cl-4-HO$(CH_2)_2$O-Ph
B48		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B49		3-Cl-4-HO-Ph
B50		3-F-4-HO-Ph
B51	4-(1-pipe)-1-pipe	2-MeO-4-Py
B52		quinolin-6-yl
B53		3-Cl-4-HO$(CH_2)_2$O-Ph
B54		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B55		3-Cl-4-HO-Ph
B56	4-(4-F-1-pipe)-1-pipe	2-MeO-4-Py
B57		quinolin-6-yl
B58		3-Cl-4-HO$(CH_2)_2$O-Ph
B59		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B60		3-Cl-4-HO-Ph
B61		2-MeO-4-Py
B62		quinolin-6-yl
B63		3-Cl-4-HO$(CH_2)_2$O-Ph
B64		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B65		3-Cl-4-HO-Ph
B66		2-MeO-4-Py
B67		quinolin-6-yl
B68		3-Cl-4-HO$(CH_2)_2$O-Ph
B69		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B70		3-Cl-4-HO-Ph
B71		2-MeO-4-Py
B72		quinolin-6-yl
B73		3-Cl-4-HO$(CH_2)_2$O-Ph
B74		5-Cl-6-HO$(CH_2)_3$NH-3-Py
B75		3-Cl-4-HO-Ph
B76		2-MeO-4-Py

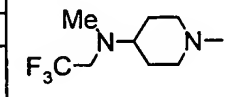
B77		quinolin-6-yl
B78		3-Cl-4-HO(CH$_2$)$_2$O-Ph
B79		5-Cl-6-HO(CH$_2$)$_3$NH-3-Py
B80		3-Cl-4-HO-Ph

[0095]

[Table 22]

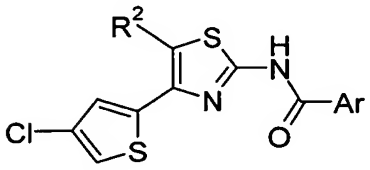


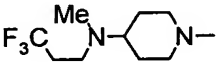
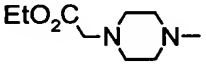
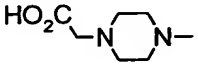
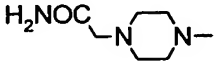
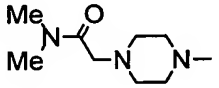
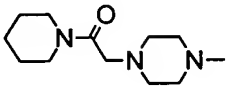
No	R^2	Ar
B81		2-MeO-4-Py
B82		qionlin-6-yl
B83		3-Cl-4-HO(CH$_2$)$_2$O-Ph
B84		5-Cl-6-HO(CH$_2$)$_3$NH-3-Py
B85		3-Cl-4-HO-Ph
B86		2-MeO-4-Py
B87		qinolin-6-yl
B88		3-Cl-4-HO(CH$_2$)$_2$O-Ph
B89		5-Cl-6-HO(CH$_2$)$_3$NH-3-Py
B90		3-Cl-4-HO-Ph
B91	4-(4-F-cHex)-1-pipa	2-MeO-4-Py
B92		qinolin-6-yl
B93		3-Cl-4-HO(CH$_2$)$_2$O-Ph
B94		5-Cl-6-HO(CH$_2$)$_3$NH-3-Py
B95		3-Cl-4-HO-Ph
B96	4-(4-MeO-cHex)-1-pipa	2-MeO-4-Py
B97		quinolin-6-yl
B98		3-Cl-4-HO(CH$_2$)$_2$O-Ph
B99		5-Cl-6-HO(CH$_2$)$_3$NH-3-Py
B100		3-Cl-4-HO-Ph
B101	4-(4-CF3-cHex)-1-pipa	2-MeO-4-Py
B102		quinolin-6-yl
B103		3-Cl-4-HO(CH2)2O-Ph
B104		5-Cl-6-HO(CH2)3NH-3-Py
B105		3-Cl-4-HO-Ph
B106		2-MeO-4-Py
B107		quinolin-6-yl
B108		3-Cl-4-HO(CH2)2O-Ph
B109		5-Cl-6-HO(CH2)3NH-3-Py
B110		3-Cl-4-HO-Ph
B111		2-MeO-4-Py
B112		quinolin-6-yl
B113		3-Cl-4-HO(CH2)2O-Ph
B114		5-Cl-6-HO(CH2)3NH-3-Py
B115		3-Cl-4-HO-Ph
B116		2-MeO-4-Py
B117		quinolin-6-yl

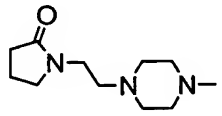
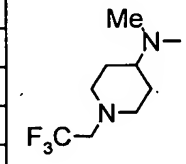
B118		3-Cl-4-HO(CH2)2O-Ph
B119		5-Cl-6-HO(CH2)3NH-3-Py
B120		3-Cl-4-HO-Ph

[0096]

[Table 23]

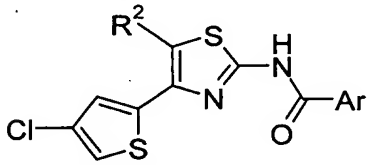


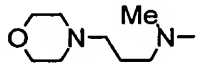
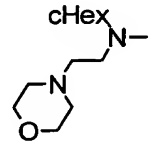
No	R^2	Ar
C1		2-MeO-4-Py
C2		quinolin-6-yl
C3		3-Cl-4-HO(CH_2)$_2$O-Ph
C4		5-Cl-6-HO(CH_2)$_3$NH-3-Py
C5		3-Cl-4-HO-Ph
C6		2-MeO-4-Py
C7		quinolin-6-yl
C8		3-Cl-4-HO(CH_2)$_2$O-Ph
C9		5-Cl-6-HO(CH_2)$_3$NH-3-Py
C10		3-Cl-4-HO-Ph
C11		2-MeO-4-Py
C12		quinolin-6-yl
C13		3-Cl-4-HO(CH_2)$_2$O-Ph
C14		5-Cl-6-HO(CH_2)$_3$NH-3-Py
C15		3-Cl-4-HO-Ph
C16		2-MeO-4-Py
C17		quinolin-6-yl
C18		3-Cl-4-HO(CH_2)$_2$O-Ph
C19		5-Cl-6-HO(CH_2)$_3$NH-3-Py
C20		3-Cl-4-HO-Ph
C21		2-MeO-4-Py
C22		quinolin-6-yl
C23		3-Cl-4-HO(CH_2)$_2$O-Ph
C24		5-Cl-6-HO(CH_2)$_3$NH-3-Py
C25		3-Cl-4-HO-Ph
C26		2-MeO-4-Py
C27		quinolin-6-yl
C28		3-Cl-4-HO(CH_2)$_2$O-Ph
C29		5-Cl-6-HO(CH_2)$_3$NH-3-Py
C30		3-Cl-4-HO-Ph
C31		2-MeO-4-Py
C32		quinolin-6-yl
C33		3-Cl-4-HO(CH_2)$_2$O-Ph
C34		5-Cl-6-HO(CH_2)$_3$NH-3-Py

C35		3-Cl-4-HO-Ph
C36		2-MeO-4-Py
C37		quinolin-6-yl
C38		3-Cl-4-HO(CH_2)$_2$O-Ph
C39		5-Cl-6-HO(CH_2)$_3$NH-3-Py
C40		3-Cl-4-HO-Ph

[0097]

[Table 24]

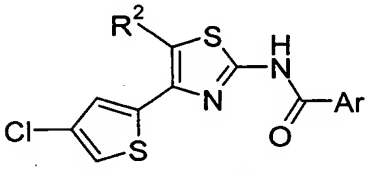


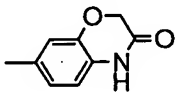
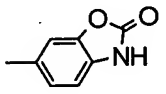
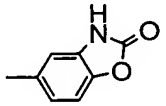
No	R^2	Ar
C41		quinolin-6-yl
C42		3-Cl-4-HO(CH_2)$_2$O-Ph
C43		5-Cl-6-HO(CH_2)$_3$NH-3-Py
C44		3-Cl-4-HO-Ph
C45		quinolin-6-yl
C46		3-Cl-4-HO(CH_2)$_2$O-Ph
C47		5-Cl-6-HO(CH_2)$_3$NH-3-Py
C48		3-Cl-4-HO-Ph
C49		2-MeO-4-Py
C50		quinolin-6-yl
C51		3-Cl-4-HO(CH2)2O-Ph
C52		5-Cl-6-HO(CH2)3NH-3-Py
C53		3-Cl-4-HO-Ph
C54	1-pipe	2-MeO-4-Py
C55		quinolin-6-yl
C56		3-Cl-4-HO(CH2)2O-Ph
C57		5-Cl-6-HO(CH2)3NH-3-Py
C58		3-Cl-4-HO-Ph
C59	4-F-1-pipe	2-MeO-4-Py
C60		quinolin-6-yl
C61		3-Cl-4-HO(CH2)2O-Ph
C62		5-Cl-6-HO(CH2)3NH-3-Py
C63		3-Cl-4-HO-Ph
C64	3-(Me2NCH2)-1-pipe	2-MeO-4-Py
C65		quinolin-6-yl
C66		3-Cl-4-HO(CH2)2O-Ph
C67		5-Cl-6-HO(CH2)3NH-3-Py
C68		3-Cl-4-HO-Ph

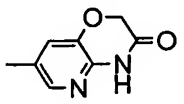
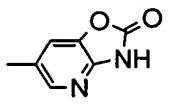
C69	2-(Me2NCH2)-1-pipe	2-MeO-4-Py
C70		quinolin-6-yl
C71		3-Cl-4-HO(CH2)2O-Ph
C72		5-Cl-6-HO(CH2)3NH-3-Py
C73		3-Cl-4-HO-Ph

[0098]

[Table 25]

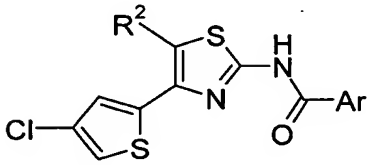


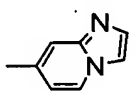
No	R^2	Ar
C74	4-cHex-1-pipa	2-hydroxyquinolin-6-yl
C75	4-nPr-1-pipa	
C76	4-nPr-1-pipe	
C77	4-cHex-1-pipa	3-hydroxyquinolin-7-yl
C78	4-nPr-1-pipa	
C79	4-nPr-1-pipe	
C80	4-cHex-1-pipa	7-hydroxyquinolin-3-yl
C81	4-nPr-1-pipa	
C82	4-nPr-1-pipe	
C83	4-cHex-1-pipa	2-methoxycarbonylquinolin-6-yl
C84	4-nPr-1-pipa	
C85	4-nPr-1-pipe	
C86	4-cHex-1-pipa	2-carboxyquinolin-6-yl
C87	4-nPr-1-pipa	
C88	4-nPr-1-pipe	
C89	4-nPr-1-pipa	2-carbamoylquinolin-6-yl
C90	4-nPr-1-pipe	
C91	4-cHex-1-pipa	2-hydroxymethylquinolin-6-yl
C92	4-nPr-1-pipa	
C93	4-nPr-1-pipe	
C94	4-cHex-1-pipa	2-methoxymethylquinolin-6-yl
C95	4-nPr-1-pipa	
C96	4-nPr-1-pipe	
C97	4-nPr-1-pipa	
C98	4-nPr-1-pipe	
C99	4-nPr-1-pipa	
C100	4-nPr-1-pipe	
C101	4-cHex-1-pipa	
C102	4-nPr-1-pipa	
C103	4-nPr-1-pipe	

C104	4-cHex-1-pipa	
C105	4-nPr-1-pipa	
C106	4-nPr-1-pipe	
C107	4-cHex-1-pipa	
C108	4-nPr-1-pipa	
C109	4-nPr-1-pipe	
C110	4-nPr-1-pipa	isoquinolin-6-yl
C111	4-nPr-1-pipe	
C112	4-cHex-1-pipa	isoquinolin-7-yl
C113	4-nPr-1-pipa	
C114	4-nPr-1-pipe	

[0099]

[Table 26]

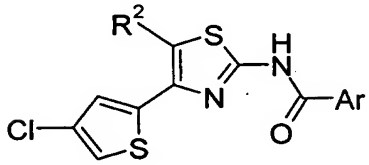


No	R^2	Ar
D1	4-cHex-1-pipa	quinolin-7-yl
D2	4-nPr-1-pipa	
D3	4-nPr-1-pipe	
D4	4-cHex-1-pipa	quinolin-3-yl
D5	4-nPr-1-pipa	
D6	4-nPr-1-pipe	
D7	4-cHex-1-pipa	2-hydroxyquinoxalin-6-yl
D8	4-nPr-1-pipa	
D9	4-nPr-1-pipe	
D10	4-cHex-1-pipa	benzoxazol-6-yl
D11	4-nPr-1-pipa	
D12	4-nPr-1-pipe	
D13	4-cHex-1-pipa	1-methyl-1,2,3,4-tetrahydroquinolin-6-yl
D14	4-nPr-1-pipa	
D15	4-nPr-1-pipe	
D16	4-cHex-1-pipa	1-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl
D17	4-nPr-1-pipa	
D18	4-nPr-1-pipe	
D19	4-cHex-1-pipa	
D20	4-nPr-1-pipa	
D21	4-nPr-1-pipe	
D22	4-cHex-1-pipa	1-methyl-3,4-dihydro-2H-1,4-benzoxazin-7-yl
D23	4-nPr-1-pipa	
D24	4-nPr-1-pipe	
D25	4-cHex-1-pipa	3-F-4-$HOCH_2CH_2O$-Ph
D26	4-nPr-1-pipa	

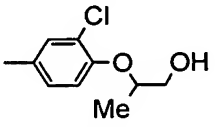
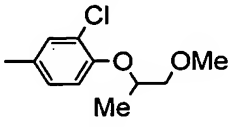
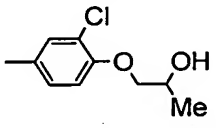
D27	4-nPr-1-pipe	
D28	4-nPr-1-pipa	3-Br-4-$HOCH_2CH_2O$-Ph
D29	4-nPr-1-pipe	
D30	4-cHex-1-pipa	3-Me-4-$HOCH_2CH_2O$-Ph
D31	4-nPr-1-pipa	
D32	4-nPr-1-pipe	
D33	4-cHex-1-pipa	3-CF3-4-$HOCH_2CH_2O$-Ph
D34	4-nPr-1-pipa	
D35	4-nPr-1-pipe	
D36	4-cHex-1-pipa	3,5-diF-4-$HOCH_2CH_2O$-Ph
D37	4-nPr-1-pipa	
D38	4-nPr-1-pipe	
D39	4-nPr-1-pipa	3,5-diCl-4-$HOCH_2CH_2O$-Ph
D40	4-nPr-1-pipe	
D41	4-nPr-1-pipa	3-Cl-5-F-4-$HOCH_2CH_2O$-Ph
D42	4-nPr-1-pipe	

[0100]

[Table 27]

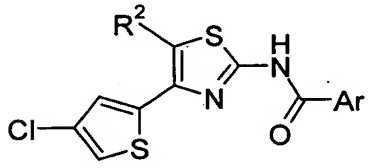


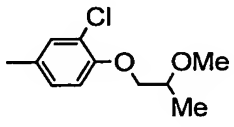
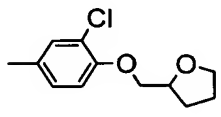
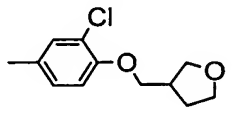
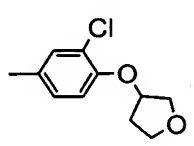
No	R^2	Ar
D43	4-cHex-1-pipa	3-F-4-$MeOCH_2CH_2O$-Ph
D44	4-nPr-1-pipa	
D45	4-nPr-1-pipe	
D46	4-cHex-1-pipa	3-Br-4-$MeOCH_2CH_2O$-Ph
D47	4-nPr-1-pipa	
D48	4-nPr-1-pipe	
D49	4-cHex-1-pipa	3-Me-4-$MeOCH_2CH_2O$-Ph
D50	4-nPr-1-pipa	
D51	4-nPr-1-pipe	
D52	4-cHex-1-pipa	3-CF3-4-$MeOCH_2CH_2O$-Ph
D53	4-nPr-1-pipa	
D54	Mor	
D55	4-nPr-1-pipa	3-Cl-4-$HOCH_2CH_2CH_2O$-Ph
D56	4-nPr-1-pipe	
D57	4-cHex-1-pipa	3-Cl-5-F-4-$HOCH_2CH_2CH_2O$-Ph
D58	4-nPr-1-pipa	
D59	4-nPr-1-pipe	
D60	4-cHex-1-pipa	3,5-diF-4-HOCH2CH2CH2O-Ph
D61	4-nPr-1-pipa	
D62	4-nPr-1-pipe	
D63	4-cHex-1-pipa	3-Cl-4-MeOCH2CH2CH2O-Ph
D64	4-nPr-1-pipa	
D65	4-nPr-1-pipe	
D66	4-nPr-1-pipa	3-Cl-4-HO-Ph
D67	4-nPr-1-pipe	

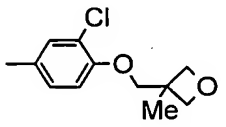
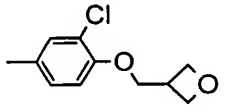
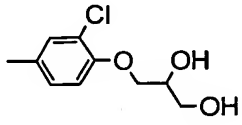
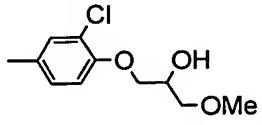
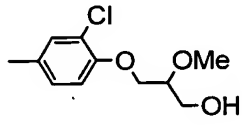
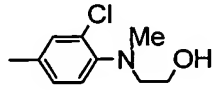
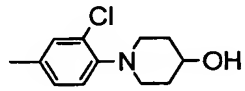
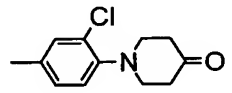
D68	4-cHex-1-pipa	3,5-diF-4-HO-Ph
D69	4-nPr-1-pipa	
D70	4-nPr-1-pipe	
D71	4-cHex-1-pipa	3-Cl-5-F-4-HO-Ph
D72	4-nPr-1-pipa	
D73	4-nPr-1-pipe	
D74	4-cHex-1-pipa	3,5-diCl-4-HO-Ph
D75	4-nPr-1-pipa	
D76	4-nPr-1-pipe	
D77	4-nPr-1-pipa	
D78	4-nPr-1-pipe	
D79	4-cHex-1-pipa	
D80	4-nPr-1-pipa	
D81	4-nPr-1-pipe	
D82	4-cHex-1-pipa	
D83	4-nPr-1-pipa	
D84	4-nPr-1-pipe	

[0101]

[Table 28]

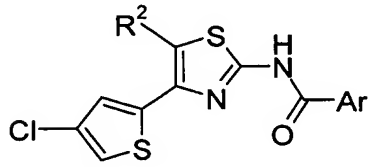


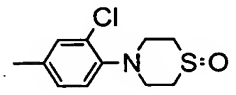
No	R^2	Ar
D85	4-cHex-1-pipa	
D86	4-nPr-1-pipa	
D87	4-nPr-1-pipe	
D88	4-cHex-1-pipa	
D89	4-nPr-1-pipa	
D90	4-nPr-1-pipe	
D91	4-cHex-1-pipa	
D92	4-nPr-1-pipa	
D93	4-nPr-1-pipe	
D94	4-cHex-1-pipa	
D95	4-nPr-1-pipa	
D96	4-nPr-1-pipe	

D97	4-cHex-1-pipa	
D98	4-nPr-1-pipa	
D99	4-nPr-1-pipe	
D100	4-cHex-1-pipa	
D101	4-nPr-1-pipa	
D102	4-nPr-1-pipe	
D103	4-cHex-1-pipa	
D104	4-nPr-1-pipa	
D105	4-nPr-1-pipe	
D106	4-cHex-1-pipa	
D107	4-nPr-1-pipa	
D108	4-nPr-1-pipe	
D109	4-cHex-1-pipa	
D110	4-nPr-1-pipa	
D111	4-nPr-1-pipe	
D112	4-cHex-1-pipa	
D113	4-nPr-1-pipa	
D114	4-nPr-1-pipe	
D115	4-cHex-1-pipa	
D116	4-nPr-1-pipa	
D117	4-nPr-1-pipe	
D118	4-cHex-1-pipa	
D119	4-nPr-1-pipa	
D120	4-nPr-1-pipe	

[0102]

[Table 29]

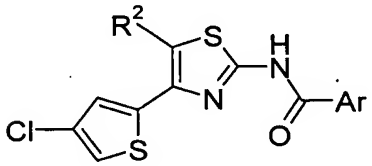


No	R^2	Ar
E1	4-cHex-1-pipa	
E2	4-nPr-1-pipa	
E3	4-nPr-1-pipe	
E4	4-cHex-1-pipa	3-F-4-(4-EtO_2C-1-pipe)-Ph
E5	4-nPr-1-pipa	

E6	4-nPr-1-pipe	
E7	4-cHex-1-pipa	3-F-4-(4-H_2NOC-1-pipe)-Ph
E8	4-nPr-1-pipa	
E9	4-nPr-1-pipe	
E10	4-cHex-1-pipa	3-F-4-(4-HO_2C-1-pipe)-Ph
E11	4-nPr-1-pipa	
E12	4-nPr-1-pipe	
E13	4-cHex-1-pipa	3-Cl-4-(4-EtO_2C-1-pipe)-Ph
E14	4-nPr-1-pipa	
E15	4-nPr-1-pipe	
E16	4-cHex-1-pipa	3-Cl-4-(4-H_2NOC-1-pipe)-Ph
E17	4-nPr-1-pipa	
E18	4-nPr-1-pipe	
E19	4-cHex-1-pipa	3-Cl-4-(4-HO2C-1-pipe)-Ph
E20	4-nPr-1-pipa	
E21	4-nPr-1-pipe	
E22	4-cHex-1-pipa	3-Br-4-(4-EtO2C-1-pipe)-Ph
E23	4-nPr-1-pipa	
E24	4-nPr-1-pipe	
E25	4-cHex-1-pipa	3-Br-4-(4-H2NOC-1-pipe)-Ph
E26	4-nPr-1-pipa	
E27	4-nPr-1-pipe	
E28	4-cHex-1-pipa	3-Br-4-(4-HO2C-1-pipe)-Ph
E29	4-nPr-1-pipa	
E30	4-nPr-1-pipe	
E31	4-cHex-1-pipa	3,5-diF-4-(4-EtO2C-1-pipe)-Ph
E32	4-nPr-1-pipa	
E33	4-nPr-1-pipe	
E34	4-cHex-1-pipa	3,5-diF-4-(4-H2NOC-1-pipe)-Ph
E35	4-nPr-1-pipa	
E36	4-nPr-1-pipe	
E37	4-cHex-1-pipa	3,5-diF-4-(4-HO2C-1-pipe)-Ph
E38	4-nPr-1-pipa	
E39	4-nPr-1-pipe	
E40	4-cHex-1-pipa	3-Cl-5-F-4-(4-EtO2C-1-pipe)-Ph
E41	4-nPr-1-pipa	
E42	4-nPr-1-pipe	
E43	4-cHex-1-pipa	3-Cl-5-F-4-(4-H2NOC-1-pipe)-Ph
E44	4-nPr-1-pipa	
E45	4-nPr-1-pipe	

[0103]

[Table 30]

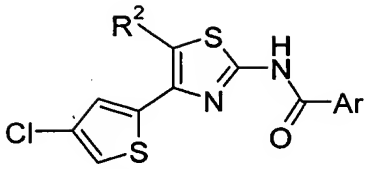


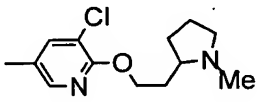
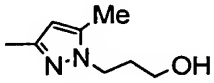
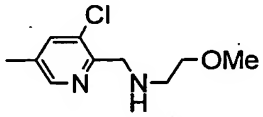
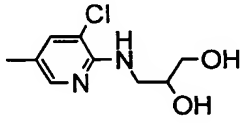
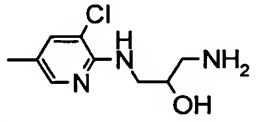
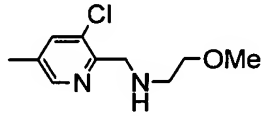
No	R^2	Ar
E46	4-cHex-1-pipa	3-Cl-5-F-4-(4-HO_2C-1-pipe)-Ph

E47	4-nPr-1-pipa	
E48	4-nPr-1-pipe	
E49	4-cHex-1-pipa	3-Cl-4-H_2NOCCH_2O-Ph
E50	4-nPr-1-pipa	
E51	4-nPr-1-pipe	
E52	4-cHex-1-pipa	3-Cl-4-$H_2NCH_2CH_2O$-Ph
E53	4-nPr-1-pipa	
E54	4-nPr-1-pipe	
E55	4-nPr-1-pipa	5-Cl-6-$HOCH_2CH_2O$-3-Py
E56	4-nPr-1-pipe	
E57	4-cHex-1-pipa	5-Cl-6-$MeOCH_2CH_2O$-3-Py
E58	4-nPr-1-pipa	
E59	4-nPr-1-pipe	
E60	4-nPr-1-pipa	5-Cl-6-$HOCH_2CH_2CH_2O$-3-Py
E61	4-nPr-1-pipe	
E62	4-cHex-1-pipa	5-Cl-6-$MeOCH_2CH_2CH_2O$-3-Py
E63	4-nPr-1-pipa	
E64	4-nPr-1-pipe	
E65	4-nPr-1-pipa	5-Cl-6-$HOCH_2CH_2CH_2NH$-3-Py
E66	4-nPr-1-pipe	
E67	4-cHex-1-pipa	5-Cl-6-$MeOCH_2CH_2CH_2NH$-3-Py
E68	4-nPr-1-pipa	
E69	4-nPr-1-pipe	
E70	4-cHex-1-pipa	5-Cl-6-$H_2NCH_2CH_2CH_2NH$-3-Py
E71	4-nPr-1-pipa	
E72	4-nPr-1-pipe	
E73	4-nPr-1-pipa	5-Cl-6-$HOCH_2CH_2NH$-3-Py
E74	4-nPr-1-pipe	
E75	4-nPr-1-pipa	5-Cl-6-$MeOCH_2CH_2NH$-3-Py
E76	4-nPr-1-pipe	
E77	4-cHex-1-pipa	5-Cl-6-$H_2NCH_2CH_2NH$-3-Py
E78	4-nPr-1-pipa	
E79	4-nPr-1-pipe	
E80	4-nPr-1-pipa	5-Cl-6-$HOCH_2CH_2N(Me)$-3-Py
E81	4-nPr-1-pipe	
E82	4-cHex-1-pipa	5-Cl-6-$MeOCH_2CH_2N(Me)$-3-Py
E83	4-nPr-1-pipa	
E84	4-nPr-1-pipe	
E85	4-cHex-1-pipa	5-Cl-6-$HOCH_2CH_2CH_2N(Me)$-3-Py
E86	4-nPr-1-pipa	
E87	4-nPr-1-pipe	
E88	4-cHex-1-pipa	5-Cl-6-$MeOCH_2CH_2CH_2N(Me)$-3-Py
E89	4-nPr-1-pipa	
E90	4-nPr-1-pipe	

[0104]

[Table 31]

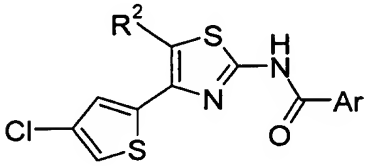


No	R^2	Ar
F1	4-cHex-1-pipa	2-$HOCH_2CH_2O$-4-Py
F2	4-nPr-1-pipa	
F3	4-nPr-1-pipe	
F4	4-cHex-1-pipa	2-$MeOCH_2CH_2O$-4-Py
F5	4-nPr-1-pipa	
F6	4-nPr-1-pipe	
F7	4-cHex-1-pipa	
F8	4-nPr-1-pipa	
F9	4-nPr-1-pipe	
F10	4-nPr-1-pipa	
F11	4-nPr-1-pipe	
F12	4-cHex-1-pipa	
F13	4-nPr-1-pipa	
F14	4-nPr-1-pipe	
F15	4-cHex-1-pipa	5-Cl-6-HOCH(Me)CH2NH-3-Py
F16	4-nPr-1-pipa	
F17	4-nPr-1-pipe	
F18	4-cHex-1-pipa	
F19	4-nPr-1-pipa	
F20	4-nPr-1-pipe	
F21	4-cHex-1-pipa	
F22	4-nPr-1-pipa	
F23	4-nPr-1-pipe	
F24	4-cHex-1-pipa	
F25	4-nPr-1-pipa	
F26	4-nPr-1-pipe	
F27	4-cHex-1-pipa	5-Cl-6-HOCH(Me)CH2NH-3-Py
F28	4-nPr-1-pipa	
F29	4-nPr-1-pipe	
F30	4-cHex-1-pipa	5-Cl-6-HOCH(Me)CH2NH-3-Py
F31	4-nPr-1-pipa	
F32	4-nPr-1-pipe	
F33	4-cHex-1-pipa	5-Cl-6-(HOCH2CH2)2N-3-Py
F34	4-nPr-1-pipa	
F35	4-nPr-1-pipe	
F36	4-cHex-1-pipa	5-Cl-6-(4-HO-cHex)NH-3-Py

F37	4-nPr-1-pipa	
F38	4-nPr-1-pipe	
F39	4-cHex-1-pipa	5-Cl-6-(3-HO-cHex)NH-3-Py
F40	4-nPr-1-pipa	
F41	4-nPr-1-pipe	

[0105]

[Table 32]

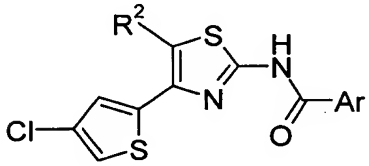


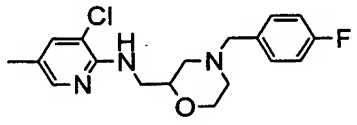
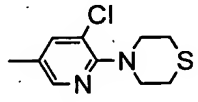
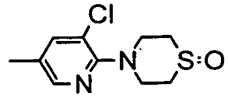
No	R^2	Ar
F42	4-cHex-1-pipa	5-Cl-6-(2-HO-cHex)NH-3-Py
F43	4-nPr-1-pipa	
F44	4-nPr-1-pipe	
F45	4-nPr-1-pipa	5-Cl-6-(4-HO-1-pipe)-3-Py
F46	4-nPr-1-pipe	
F47	4-cHex-1-pipa	5-Cl-6-(3-HO-1-pipe)-3-Py
F48	4-nPr-1-pipa	
F49	4-nPr-1-pipe	
F50	4-cHex-1-pipa	5-Cl-6-(4-$HOCH_2$-1-pipe)-3-Py
F51	4-nPr-1-pipa	
F52	4-nPr-1-pipe	
F53	4-cHex-1-pipa	5-Cl-6-(3-$HOCH_2$-1-pipe)-3-Py
F54	4-nPr-1-pipa	
F55	4-nPr-1-pipe	
F56	4-cHex-1-pipa	5-Cl-6-(2-$HOCH_2CH_2$-1-pipe)-3-Py
F57	4-nPr-1-pipa	
F58	4-nPr-1-pipe	
F59	4-cHex-1-pipa	5-Cl-6-(4-benzylamino-1-pipe)-3-Py
F60	4-nPr-1-pipa	
F61	4-nPr-1-pipe	
F62	4-cHex-1-pipa	5-Cl-6-(4-MeO-1-pipe)-3-Py
F63	4-nPr-1-pipa	
F64	4-nPr-1-pipe	
F65	4-cHex-1-pipa	5-Cl-6-(4-F-1-pipe)-3-Py
F66	4-nPr-1-pipa	
F67	4-nPr-1-pipe	
F68	4-nPr-1-pipa	5-Cl-6-(4-EtO2C-1-pipe)-3-Py
F69	4-nPr-1-pipe	
F70	4-nPr-1-pipa	5-Cl-6-(4-H2NOC-1-pipe)-3-Py
F71	4-nPr-1-pipe	
F72	4-nPr-1-pipa	5-Cl-6-(4-HO2C-1-pipe)-3-Py
F73	4-nPr-1-pipe	
F74	4-cHex-1-pipa	5-Cl-6-EtO2CCH2NH-3-Py
F75	4-nPr-1-pipa	
F76	4-nPr-1-pipe	
F77	4-cHex-1-pipa	5-Cl-6-H2NOCCH2NH-3-Py

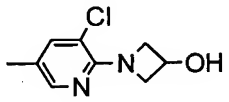
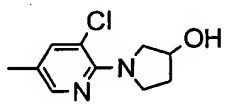
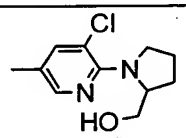
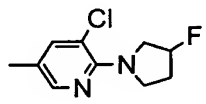
F78	4-nPr-1-pipa	
F79	4-nPr-1-pipe	
F80	4-cHex-1-pipa	5-Cl-6-HO2CCH2NH-3-Py
F81	4-nPr-1-pipa	
F82	4-nPr-1-pipe	

[0106]

[Table 33]

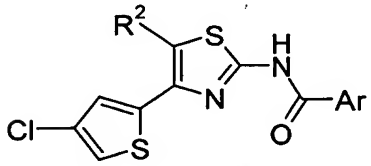


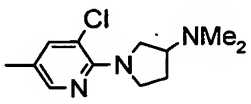
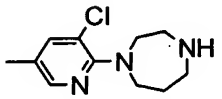
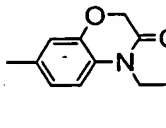
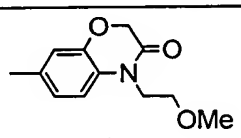
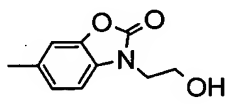
No	R^2	Ar
F83	4-cHex-1-pipa	5-Cl-6-(1-pipa)-3-Py
F84	4-nPr-1-pipa	
F85	4-nPr-1-pipe	
F86	4-cHex-1-pipa	5-Cl-6-(4-$MeOCH_2CH_2$-1-pipa)-3-Py
F87	4-nPr-1-pipa	
F88	4-nPr-1-pipe	
F89	4-cHex-1-pipa	5-Cl-6-(4-$HOCH_2CH_2$-1-pipa)-3-Py
F90	4-nPr-1-pipa	
F91	4-nPr-1-pipe	
F92	4-cHex-1-pipa	5-Cl-6-(3-$HOCH_2$-4-Me-1-pipa)-3-Py
F93	4-nPr-1-pipa	
F94	4-nPr-1-pipe	
F95	4-nPr-1-pipa	5-Cl-6-(3-oxo-1-pipa)-3-Py
F96	4-nPr-1-pipe	
F97	4-cHex-1-pipa	5-Cl-6-Mor-3-Py
F98	4-nPr-1-pipa	
F99	4-nPr-1-pipe	
F100	4-cHex-1-pipa	5-Cl-6-(2-$HOCH_2$-Mor)-3-Py
F101	4-nPr-1-pipa	
F102	4-nPr-1-pipe	
F103	4-cHex-1-pipa	
F104	4-nPr-1-pipa	
F105	4-nPr-1-pipe	
F106	4-cHex-1-pipa	
F107	4-nPr-1-pipa	
F108	4-nPr-1-pipe	
F109	4-cHex-1-pipa	
F110	4-nPr-1-pipa	
F111	4-nPr-1-pipe	
F112	4-cHex-1-pipa	
F113	4-nPr-1-pipa	

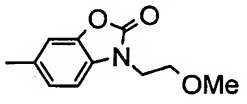
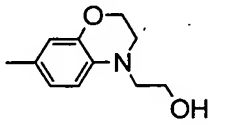
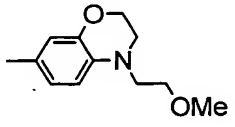
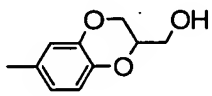
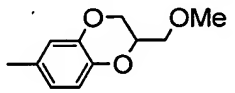
F114	4-nPr-1-pipe	
F115	4-cHex-1-pipa	
F116	4-nPr-1-pipa	
F117	4-nPr-1-pipe	
F118	4-cHex-1-pipa	
F119	4-nPr-1-pipa	
F120	4-nPr-1-pipe	
F121	4-cHex-1-pipa	
F122	4-nPr-1-pipa	
F123	4-nPr-1-pipe	

[0107]

[Table 34]

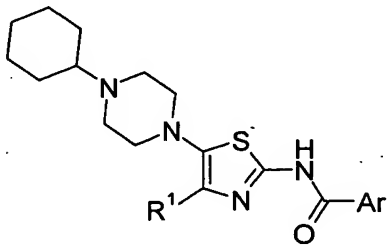


No	R^2	Ar
G1	4-cHex-1-pipa	
G2	4-nPr-1-pipa	
G3	4-nPr-1-pipe	
G4	4-cHex-1-pipa	
G5	4-nPr-1-pipa	
G6	4-nPr-1-pipe	
G7	4-cHex-1-pipa	
G8	4-nPr-1-pipa	
G9	4-nPr-1-pipe	
G10	4-cHex-1-pipa	
G11	4-nPr-1-pipa	
G12	4-nPr-1-pipe	
G13	4-cHex-1-pipa	
G14	4-nPr-1-pipa	
G15	4-nPr-1-pipe	
G16	4-cHex-1-pipa	

G17	4-nPr-1-pipa	
G18	4-nPr-1-pipe	
G19	4-cHex-1-pipa	
G20	4-nPr-1-pipa	
G21	4-nPr-1-pipe	
G22	4-cHex-1-pipa	
G23	4-nPr-1-pipa	
G24	4-nPr-1-pipe	
G25	4-cHex-1-pipa	
G26	4-nPr-1-pipa	
G27	4-nPr-1-pipe	
G28	4-cHex-1-pipa	
G29	4-nPr-1-pipa	
G30	4-nPr-1-pipe	

[0108]

[Table 35]

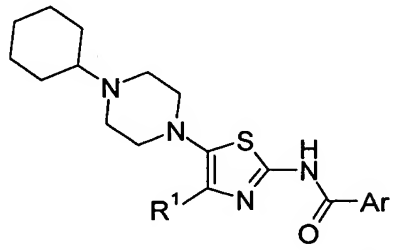


No	R^1	Ar
G31	4-methyl-2-furanyl	3-chloro-4-(2-hydroxyethoxy)phenyl
G32	1-methylpyrrol-3-yl	
G33	4-methylthiazol-2-yl	
G34	4-chlorothiazol-2-yl	
G35	4-trifluorothiazol-2-yl	
G36	5-methylthiazol-2-yl	
G37	2-methylthiazol-5-yl	
G38	5-methyloxazol-2-yl	
G39	2-methyloxazol-5-yl	
G40	4-methyl-1H-imidazol-2-yl	
G41	2-methyl-1H-imidazol-4-yl	
G42	1-methyl-1H-imidazol-4-yl	
G43	5-methylisothiazol-3-yl	
G44	3-methylisothiazol-5-yl	
G45	5-methylisoxazol-3-yl	
G46	3-methylisoxazol-5-yl	3-chloro-4-(2-hydroxyethoxy)phenyl
G47	5-methyl-1H-pyrazol-3-yl	

G48	1-methyl-1H-pyrazol-4-yl	
G49	1-methyl-1H-pyrazol-3-yl	
G50	5-methyl-1,3,4-thiadiazol-2-yl	
G51	5-methyl-1,3,4-oxadiazol-2-yl	
G52	5-methyl-1H-1,3,4-triazol-2-yl	
G53	1-methyl-1H-1,2,4-triazol-3-yl	
G54	5-methyl-1,2,4-thiadiazol-3-yl	
G55	3-methyl-1,2,4-thiadiazol-5-yl	

[0109]

[Table 36]



No	R^1	Ar
G56	5-methyl-1,2,4-oxadiazol-3-yl	3-chloro-4-(2-hydroxyethoxy)phenyl
G57	3-methyl-1,2,4-oxadiazol-5-yl	
G58	1-methyl-1H-1,2,3-triazol-4-yl	
G59	4-methylthiazol-2-yl	2-methoxypyridin-4-yl
G60	4-chlorothiazol-2-yl	
G61	4-trifluromethythiazol-2-yl	
G62	4-methylthiazol-2-yl	quinolin-6-yl
G63	4-chlorothiazol-2-yl	
G64	4-trifluoromethylthiazol-2-yl	
G65	4-methylthiazol-2-yl	3-chloro-4-(2-methoxyethoxy)phenyl
G66	4-chlorothiaozl-2-yl	
G67	4-trifluoromethylthiazol-2-yl	
G68	4-methylthiazol-2-yl	3-chloro-4-hydroxyphenyl
G69	4-chlorothiazol-2-yl	
G70	4-trifluoromethylthiazol-2-yl	

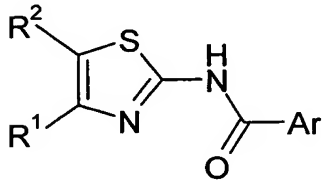
[Designation of the Document] Abstract

[Problem] To provide an excellent therapeutic agent for thrombocytopenia

[Means for Dissolution]

A 2-acylaminothiazole derivative represented by the general Formula (I) and a pharmaceutically acceptable salt thereof.

[Chemical Formula]



(I)

(wherein, Ar is optionally substituted aryl, optionally substituted monocyclic aromatic heterocycle, optionally substituted bicyclic condensed heterocycle, R1 is optionally substituted aromatic heterocycle (with the proviso that pyridyl is excluded), R2 is cyclic amino such as optionally substituted piperazine, piperidine, and the like, and linear amino.)

[Selected Drawing] No